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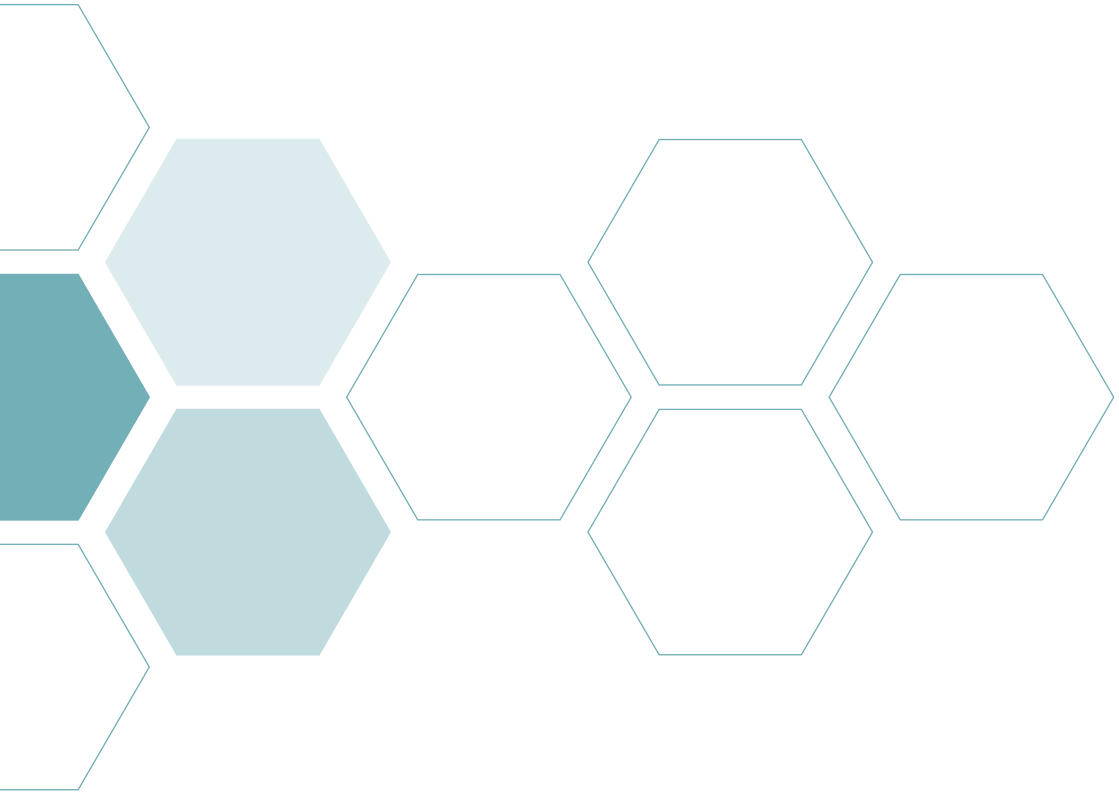

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New Frontiers in the Treatment and Management of Amyotrophic Lateral Sclerosis: Managed Care Considerations in an Evolving Treatment Paradigm

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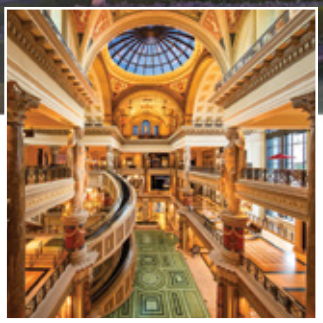

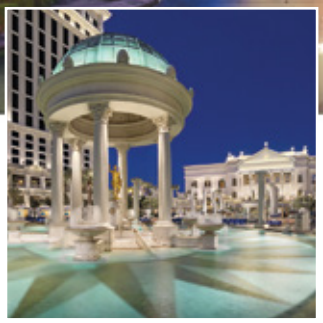

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TABLE OF CONTENTS

New Frontiers in the Treatment and Management of Amyotrophic Lateral Sclerosis (ALS): Managed Care Considerations in an Evolving Treatment Paradigm

Robert L. Sufit, MD

For a CME/CEU version of this article, please go to
http://www.namcp.org/home/education, and then click the activity title.

Summary

Although a devastating disease, there is hope for improved survival for patients with amyotrophic lateral sclerosis (ALS). Two disease-modifying therapies (DMTs), which slow the progression of the disease in addition to other interventions, have improved care for these patients. Additional agents and potentially curative gene therapies are under investigation.

Key Points

- ALS is a rare progressive neurodegenerative disorder.
- DMTs, nutritional interventions, respiratory care interventions, and aggressive symptomatic management are keys to improving quality of life and prolonging survival.

AMYOTROPHIC LATERAL SCLEROSIS (ALS) is a rare progressive neurodegenerative disorder affecting upper and lower motor neurons and bulbar neurons. It affects nerve cells in the precentral gyrus that give commands to the upper motor neurons, anterior horn cells which are the lower motor neurons that go from the spinal cord to the skeletal muscles, and the cranial nerve nuclei going to tongue, larynx and face, sometimes referred to as bulbar motor neurons. ALS is more commonly known as Lou Gehrig's disease.

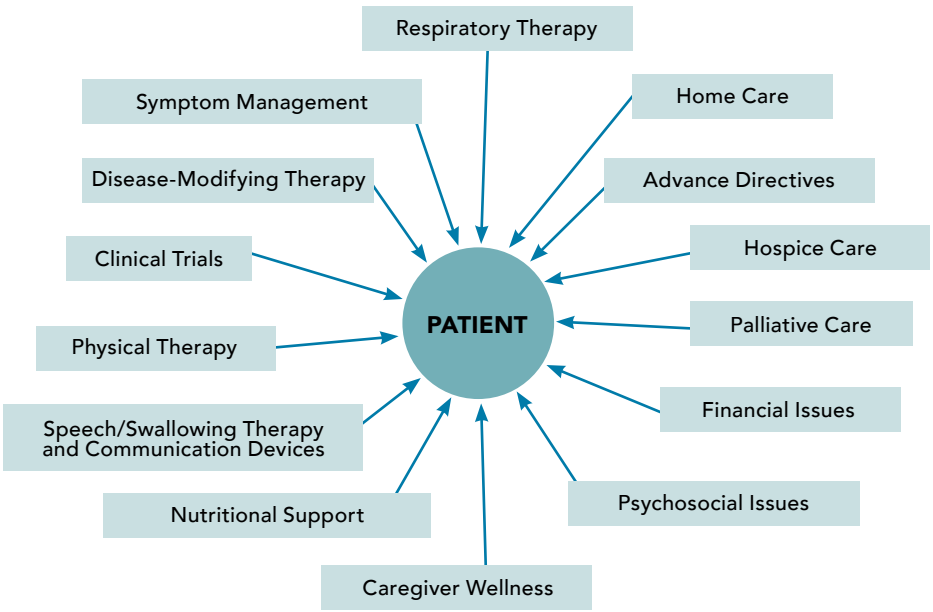
Presentation is often asymmetrical with painless weakness of one limb that is often mistaken for lumbar disc disease, carpal tunnel, or if speech is involved, stroke. Common evaluations early on include MRIs of the lumbar region, cervical spine, or brain. Initial referrals from primary care physicians may be to spine surgeons, hand surgeons, or ear nose and throat (ENT) physicians. A diagnostic delay of six or more months is not uncommon.

There has been a growing recognition over the past 20 years of more extensive involvement of the brain, specifically the prefrontal cortex and to a lesser extent the temporal lobe, in ALS. Thus, the occasional patient is first diagnosed with frontotemporal dementia (FTD) or frontotemporal lobar degeneration (FTLD). There are patients who have trouble with organization, planning, and other executive dysfunctions, or they may have motor apraxia. This is not a memory disturbance and should not be confused with clinical Alzheimer's disease. If patients live long enough with ALS, many will develop some degree of FTD or FTLD. The other problem that may arise is pseudobulbar affect (PBA), which is inappropriate involuntary laughing and crying.

Disease progression is very different among patients, with some having very rapid progression and others having a much slower disease process. It sometimes appears to plateau or even "burn out." Most patients die primarily from respiratory failure. Aspiration pneumonia, thrombosis (DVT and PE), and falls also cause morbidity and mortality.

Genetic factors cause approximately 10 percent of cases [familial ALS, (fALS)], and the rest are considered sporadic (sALS).[1] More than 30 ALS-

Exhibit 1: Managing the ALS Patient



specific genetic mutations have been identified to date. The most common is chromosome 9 open reading frame 72 (C9orf72) gene mutation, which accounts for approximately 30 to 40 percent of all fALS cases, particularly those which also have FTD. Superoxide dismutase one (SOD1) mutations account for about 20 percent of fALS cases. Many of the same gene mutations have been identified in about 17 percent of sporadic patients. Gene panels are becoming more widely used to identify fALS. The demographics of sALS are a 60 to 40 split of men to women, a median age of onset between 55 and 50, and patients tending to be otherwise healthy. For fALS, the gender split is equal, presentation is younger, and health status does not matter.

Treatment of ALS involves symptomatic management to maintain quality of life (QOL) and DMT to slow progression. Because treatment is complex and requires input from a multidisciplinary team, it is best delivered in an ALS specialty center (Exhibit 1).

Clinicians need to identify symptoms with which the patient is bothered and aggressively manage those. These can be psychological (depression, end-of-life issues, pseudobulbar affect), musculoskeletal (cramps, fasciculations), gastrointestinal, pulmonary, and others (pain, fatigue, swallowing, insomnia, drooling, communication, etc.).[2] Mobility and activities of daily living are two other major areas in which patients will need increasing levels of care as the disease progresses.

Two important survival interventions in ALS are percutaneous endoscopic gastrostomy (PEG) tubes for maintaining nutrition and noninvasive ventilation (NIV). In patients with ALS with impaired oral food intake, enteral nutrition via PEG should be considered to stabilize body weight and for prolonging survival.[3] NIV should be considered to treat respiratory insufficiency in ALS, both to lengthen survival and hopefully to slow the rate of lung function decline.[3] It also improves QOL, sleep quality, and comfort in those with respiratory insufficiency. With continued respiratory function decline, tracheostomy and invasive ventilation must be considered. Patients can continue to function with NIV. Some machines can be used during the day if a patient wants to take a bigger breath to talk and increase loudness; current models include Trilogy or Astral. Therefore, some patients will have two machines, one at night and one during the day.

Riluzole (Rilutek®, Tiglutik®) and edaravone (Radicava®) are the two FDA-approved disease modifying therapies (DMTs) approved for ALS treatment. For both drugs, the mechanism of action

in relation to ALS remains unknown; it appears to be a neuroprotective effect via inhibition of glutamatergic neurotransmission for riluzole and scavenging of free radicals for edaravone.

Riluzole was the first FDA-approved DMT for ALS (1995). It is given orally and blocks release of glutamate and modulates sodium channels. Riluzole prolongs median tracheostomy-free survival by two to three months compared to placebo in patients younger than 75 years with definite or probable ALS who have had the disease for less than five years and who have a forced vital capacity (FVC) of greater than 60 percent.[4,5] Real-world data has shown improvements in median survival times of more than 19 months.[6] The American Academy of Neurology (AAN) practice parameters state that riluzole should be offered to slow disease progression in patients with ALS (Level A evidence).[3] It is probably more effective in the early stages of the disease, and most clinicians offer this agent at the time of diagnosis. The cost of this agent is $8,000 per year for a generic and $35,000 per year for a brand name. Riluzole is a relatively well tolerated agent. Liver function tests can increase in the first few months of therapy, but typically return to normal after three months of therapy. Gastrointestinal upset can be mitigated by taking with food.

Edaravone was approved by the FDA in 2017 to slow the functional decline in patients with ALS. One trial in patients within three years of symptom onset showed no benefit over placebo, but a post hoc analysis suggested that a subset of patients with a more rapid rate of progression benefitted from treatment with edaravone.[7] The second trial was done in 137 people who showed some degree of impairment in each of the ALS Functional Rating Scale-revised (ALSFRS-R) domains, had an FVC ≥ 80 percent of expected value, were within two years of symptom onset, and had a further decline of –1 to –4 ALSFRS-R points during a 12-week observation period.[8] For this subset of patients, edaravone slowed the rate of disease progression, as measured by a decrease in ALSFRS-R score, by 33 percent at six months compared to the rate of disease progression for patients in the placebo group. In this trial, edaravone was continued open label out to 48 weeks and showed continued efficacy.[9] This agent is generally well tolerated but is given by an intravenous infusion. An initial treatment cycle is given with daily dosing for 14 days, followed by a 14-day drug-free period. Subsequent treatment cycles are daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods. Because of the need for multiple intravenous doses per month, patients require implantation of an intravenous port. The cost of edaravone is estimated to be around $148,000 per year. An oral formulation of edaravone (MT-1186) is under development.

Antisense oligonucleotides (ASOs) are under investigation for SOD1 mutated ALS. ASOs are designer drugs directed at specific genes and within the gene a specific site of action. An example is nusinersen, which is approved to treat spinal muscular atrophy. Tofersen is an ASO given by intrathecal administration that mediates the degradation of messenger RNA to reduce SOD1 protein synthesis. In a Phase I-II trial in 50 patients, cerebrospinal fluid SOD1 concentrations decreased at the highest concentration of tofersen administered intrathecally over a period of 12 weeks.[10] Since there are different SOD1 mutations, there may be need for different ASOs. For other genetic causes of ALS, there will certainly need to be different ASOs. C9orf72 is likely the next candidate, since it is more common than SOD1. Other agents under investigation are an oral tyrosine kinase inhibitor (masitinib), a humanized monoclonal antibody C5 complement inhibitor (ravulizumab-cwvz), and mesenchymal stem cell (MSC)-neurotrophic factor (NTF) cells. Gene therapy is also under investigation.

Conclusion

ALS is a rare disease of upper and lower motor neuron function along with behavioral changes. Riluzole and edaravone are used to slow the disease, but they do not stop it. Antisense therapies are being developed to slow genetic disease but need to be specific to each gene. Numerous symptom-based therapies are used to increase quality of life and survival. Because of the complicated nature of the disease, multidisciplinary care, especially in an ALS specialty center, is needed.

Robert L. Sufit, MD is a Professor of Neurology and Surgery at the Feinberg School of Medicine at Northwestern University in Chicago, IL.

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Recent Therapeutic Breakthroughs in the Treatment and Management of Pancreatic Cancer: Expert Strategies for Improved Patient Outcomes

Michael J. Pishvaian, MD, PhD

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http://www.namcp.org/home/education, and then click the activity title.

Summary

Pancreatic cancer remains one of the cancers not typically diagnosed until in the advanced or metastatic stages. Because of this, chemotherapy remains the main treatment. Targeted therapies are bringing additional hope for improved survival in those who have actionable genetic mutations or changes.

Key Points

- Standard of care chemotherapy improves overall survival and quality of life in those with advanced/metastatic disease.
- Twenty-five percent or more of pancreatic cancers have potentially highly actionable molecular biomarkers.
- All patients should have germline genetic testing.
- Virtually all patients with advanced/metastatic disease should have somatic genetic testing performed.
- Targeted therapy improves survival.
- Platinum-based chemotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors improve survival in those with DNA repair deficiencies.

IN 2021, AN ESTIMATED 60,430 PEOPLE will be diagnosed with pancreatic cancer in the United States (U.S.) and 48,220 will die.[1] The overall five-year survival rate is 10 percent. Pancreatic cancer is the fourth most common cause of cancer-related death in both men and women in the U.S. Because symptoms of this disease typically do not occur until it is advanced, most patients are diagnosed in the later stages of the cancer; few patients can be curatively resected. This cancer is already metastatic at the time of diagnosis in 45 to 55 percent of patients.

Survival of patients with metastatic pancreatic cancer is still pretty dismal (3% five-year survival rate). It has improved significantly from 5.7-month median overall survival (OS) in the late 1990s to 18 months with combination chemotherapy. National Comprehensive Cancer Network (NCCN) guideline recommendations for first-line treatment of metastatic pancreatic cancer are shown in Exhibit 1.[2] Each of these therapies are also an option for subsequent lines of therapies. In patients who are able to tolerate aggressive chemotherapy, FOLFIRINOX (5-fluorouracil/oxaliplatin/irinotecan) or gemcitabine/nab-paclitaxel are most commonly used for first-line treatment of advanced or metastatic pancreatic cancer. There are no clinical trials that directly compare these two, but a meta-analysis of 16 trials found them to produce similar OS rates, progression-free survival (PFS), and overall response rates.[3] Both regimens improve patient quality of life. Grade 3 and 4 neutropenia, febrile neutropenia, and nausea occur more often with FOLFIRINOX, and neurotoxicity and anemia occur more often with gemcitabine/nab-paclitaxel.

Exhibit 1: NCCN Preferred Regimens for First-Line Treatment of Metastatic Pancreatic Cancer[2]

Good Performance Status	Poor Performance Status
• FOLFIRINOX[a,b]	• Gemcitabine[a]
• Modified FOLFIRINOX[b]	• Capecitabine
• Gemcitabine/Nab-paclitaxel[a]	• 5-FU
• Gemcitabine/cisplatin[b]	• Pembrolizumab (only for MSI-H or dMMR tumor)
	• Larotrectinib (NTRK gene fusion positive)
	• Entrectinib (NTRK gene fusion positive, category 2B)

[a] NCCN category 1 recommendation; [b] For known BRCA 1 or 2 or PALB2 mutations

Liposomal irinotecan (Onivyde®) is one of the advances in therapy which is FDA-approved for second- or later-line therapy after gemcitabine-based treatment of metastatic pancreatic cancer. It provides higher levels of irinotecan in the blood and tumor tissue and longer exposure than free irinotecan (Camptosar®), and it is currently being studied as first-line therapy.

Predictive biomarkers are being studied to identify those patients who will benefit from specific therapies. Pancreatic cancers do harbor actionable mutations, and next-generation sequencing has consistently found that 25 percent or more of pancreatic cancers have potentially highly actionable molecular biomarkers (Exhibit 2).[4-7] Those of most interest currently are breast cancer one and two (BRCA1, BRCA2), partner and localizer of BRCA2 (PALB2), neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and microsatellite high (MSI-H) because targeted therapies are available and are supported by at least some data.

Germline testing is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes.[2] Tumor/somatic gene profiling is recommended for patients with locally advanced/metastatic disease (80% of patients) who are candidates for anti-cancer therapy to identify uncommon but actionable mutations.[2] Importantly, patients with actionable molecular alterations who receive a matched targeted therapy have significantly longer median OS than those who only receive unmatched therapies (1 year, $p = 0.0004$) or have no targetable alterations (1.3 years, $p < 0.0001$).[8]

About 1 percent of pancreatic cancer cases have MSI-H and are likely to respond to checkpoint inhibitor immunotherapy. In one small study, pembrolizumab (Keytruda®) produced a clinical tumor reduction response in four of six patients.[9] It is FDA-approved for treating MSI-H tumors.

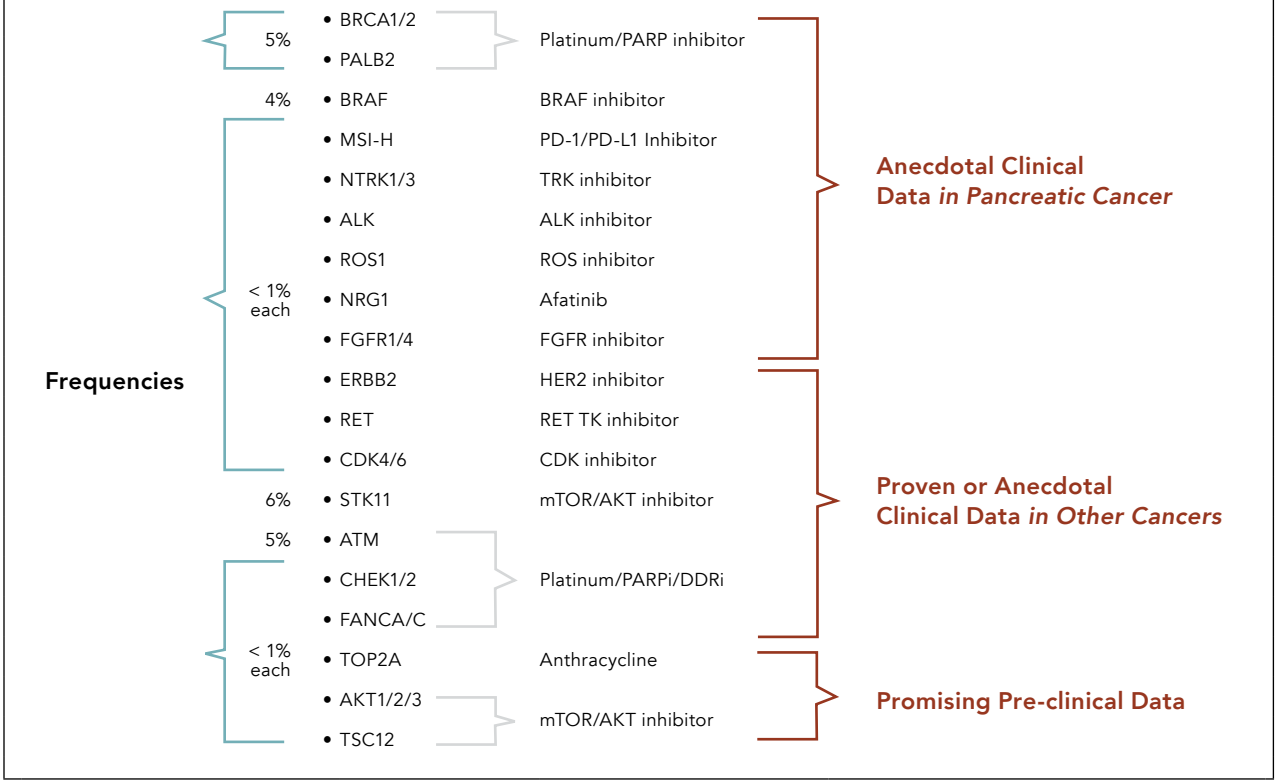
Homologous recombination DNA damage repair (HR-DDR) deficiencies occur in about 15 to 25 percent of pancreatic cancer tumors.[5,6] The better-known HR-DRR mutations associated with pancreatic cancer are BRCA1, BRCA2, PALB2, and ATM which each occur in about 5 percent of cases.

Germline BRCA 1 and 2 mutations occur in higher rates in certain populations. Those of Ashkenazi Jewish decent have a 5 percent to 16 percent rate of these two mutations.[10-12] Up to 19 percent of those with familial pancreatic cancer have one of these mutations.[12,13] Importantly, 40 percent of patients who are germline BRCA gene mutation carriers do not have a family history of pancreatic cancer.

HR-DDR mutated pancreatic cancers should be treated with platinum-based chemotherapy because of an OS advantage over non-platinum-based chemotherapy. There is a very significant one-year improvement in OS compared to HR-DDR proficient patients and compared to non-platinum-based therapy.[15] Thus, it is critical to know which patients have HR-DDR as treatment decisions are made because 50 percent of patients with pancreatic adenocarcinomas are typically treated with non-platinum-based regimens.

Germline or somatic HR deficiencies can be targeted with PARP inhibition. PARP inhibition prevents repair of single-strand DNA breaks, which leads to double-strand DNA breaks and cell death. BRCA1 and 2 are critical for DNA repair of double-strand DNA breaks via HR. Cells defective in BRCA1 and 2 and other HR-DDR genes are more

Exhibit 2: Pancreatic Cancers Harbor Actionable Mutations[4-7]



sensitive to PARP inhibition because they rely on PARP to repair DNA breaks.

Small trials or case series have been reported showing benefit of PARP inhibitors in BRCA 1/2 mutated pancreatic cancer.[14,16-18] The largest, Phase III trial published to date assessed olaparib (Lynparza®) as maintenance therapy in germline BRCA1/2 mutated pancreatic cancer after platinum-based chemotherapy. PFS at 24 months was 22.1 months in the olaparib group compared to 9.6 months in the placebo group.[19] Olaparib caused more mild fatigue, nausea, and anorexia than placebo and more patients interrupted and dose reduced olaparib but, importantly, they did not stop treatment. The NCCN guidelines recommend olaparib maintenance therapy for germline BRCA1/2 mutated disease after platinum-based chemotherapy with response or stable disease.[2] Olaparib is now FDA-approved for this indication.

Rucaparib (Rubraca®) is also being evaluated as maintenance therapy in advanced, platinum-sensitive BRCA or PALB2-related pancreatic cancer and as monotherapy in a previously treated BRCA-mutated population. Preliminary data from the maintenance trial showed there was good response (89.5% disease control rate).[20] Maintenance trials with other PARP inhibitors alone and in combination with immunotherapy are ongoing.

Less than 1 percent of pancreatic cancer cases have neurotrophic tyrosine receptor kinase (NTRK) gene fusions; however, for those who do, larotrectinib or entrectinib can produce dramatic responses.[21-22] Acquired resistance can limit the length of response. Both larotrectinib and entrectinib are FDA-approved for treating NTRK 1 and 2 gene fusion positive cancers and are consider a first-line treatment option in metastatic disease in those with poor performance status. They are not yet an option for those with good performance status because survival data is available for the chemotherapy options and not for the targeted therapies.

Conclusion

Standard of care chemotherapy improves overall survival and quality of life in those with advanced/metastatic pancreatic cancer. Actionable mutations are not rare in this disease and should be found and targeted. All patients should be germline tested and virtually all advanced patients should also have somatic testing. HR-DDR mutations are the largest

subgroup of actionable mutations. Platinum-based chemotherapy and PARP inhibitors clearly improve survival in these patients.

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Navigating the Treatment Landscape to Improve Outcomes in Psoriasis: Essential Strategies for Proper Management

April W. Armstrong, MD, MPH

For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

The biologic agents which target underlying pathophysiology of psoriasis have changed the way this disease, when moderate to severe, is treated. Whereas mild disease is still treated topically, moderate to severe disease requires a more aggressive approach with phototherapy, oral immunosuppressants, or biologics.

Key Points

- Biologic agents offer long-term safety and efficacy to those with moderate to severe psoriasis.
- They are an option for first-line treatment of moderate to severe plaque psoriasis.
- Interleukin inhibitors (IL-17 and IL-23) are the most efficacious in terms of Psoriasis Area and Severity Index (PASI) response rates and number needed to treat to achieve a PASI 75 and PASI 100.

PSORIASIS IS A CHRONIC INFLAMMATORY systemic disease with well characterized pathology occurring in the skin and often the joints. It affects 3.2 percent of United States (U.S.) adults and less than 1 percent of children.[1,2] Overall there are 8 million people with psoriasis in the U.S. It occurs with equal frequency in all genders. Seventy-five percent of cases begin before age 40. In adults, there are two peaks of onset – 20 to 30 and 40 to 50 years of age. Most children have an onset between 8 and 12.5 years of age. There is a genetic predisposition to develop psoriasis. If both parents have psoriasis, a child has a 50 percent chance of developing it.[3] If one parent has psoriasis, there is a 15 percent chance of a child developing it.

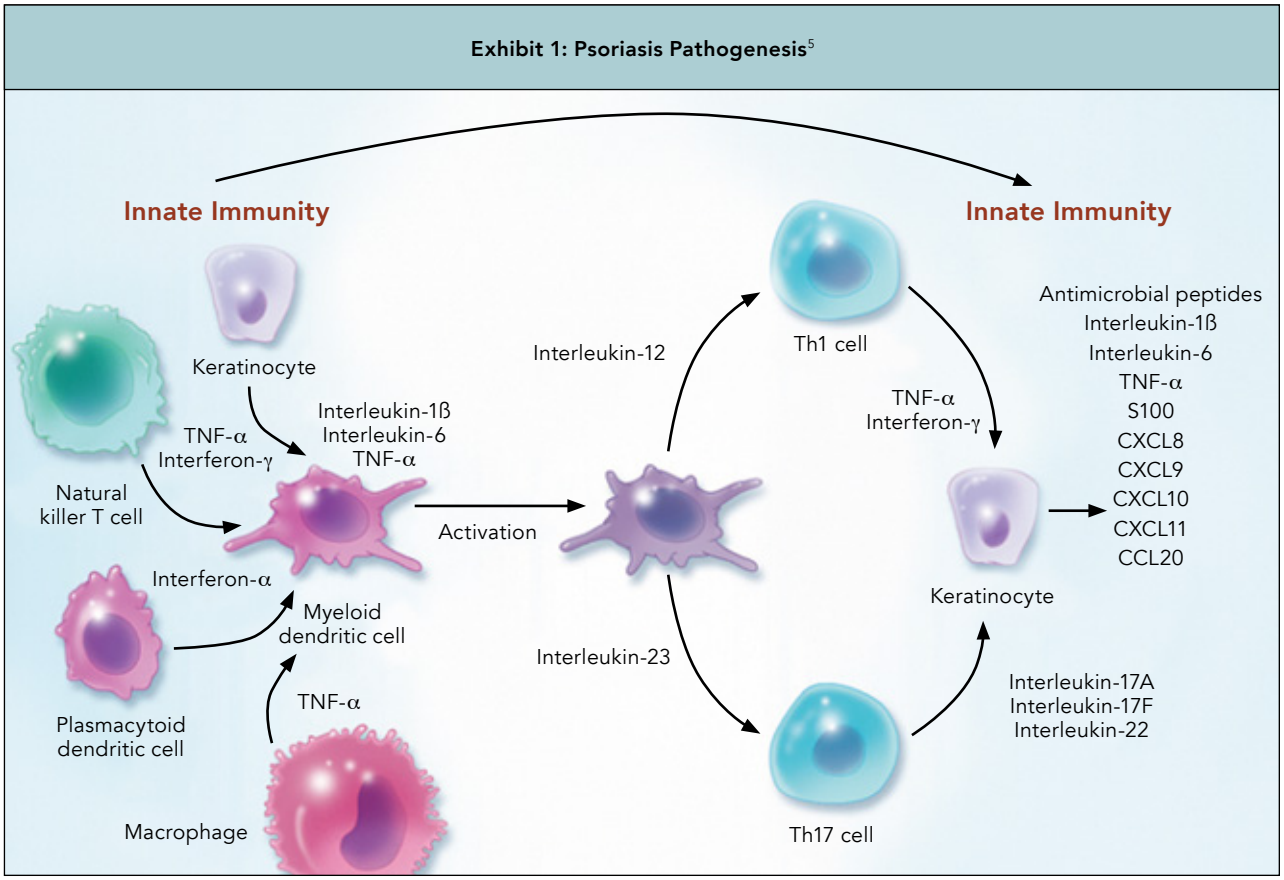
There are several different phenotypes of this disease. Plaque psoriasis is the most common (80%), but guttate, erythrodermic, pustular (generalized or palmoplantar), and inverse diseases can also occur. Palmoplantar can be especially disabling, and psoriatic nail disease can be disfiguring. Many patients can also have overlap of the phenotypes.

Plaque psoriasis is characterized by well-demarcated plaques with varying degrees of erythema (pink to red), scale (desquamation), and thickness. Guttae psoriasis is eruptive with widely distributed small red scaly papules and small plaques. It may follow streptococcal pharyngitis. Erythrodermic psoriasis has warm, red, scaly patches covering almost the entire body surface and disrupted barrier function leading to temperature, fluids, and electrolyte issues.

The differential diagnosis includes drug reaction, cutaneous T-cell lymphoma, and atopic dermatitis. Inverse psoriasis is also called intertriginous because it involves skin folds. There are smooth, well-demarcated red patches and scale is minimal or entirely absent. The affected areas are sometimes eroded and moist. This type is most often mistaken for a dermatophyte or candidal infection.

Palmoplantar psoriasis is an entity with a varying morphology, ranging from predominantly pustular lesions to thick, hyperkeratotic plaques, often with overlapping features. When this condition

Exhibit 1: Psoriasis Pathogenesis[5]



is isolated to the hands and feet it is sometimes difficult to distinguish it from hand eczema as these two conditions have many overlapping features. The pustular variant, called palmoplantar pustulosis, is regarded by many as a distinct entity, since it is not associated with HLA-Cw6, the main genetic determinant of plaque psoriasis. It is strongly associated with tobacco use and can be very challenging to treat. However, it is associated with plaque lesions elsewhere in 20 percent of patients and should still be considered part of the spectrum of psoriatic disease.

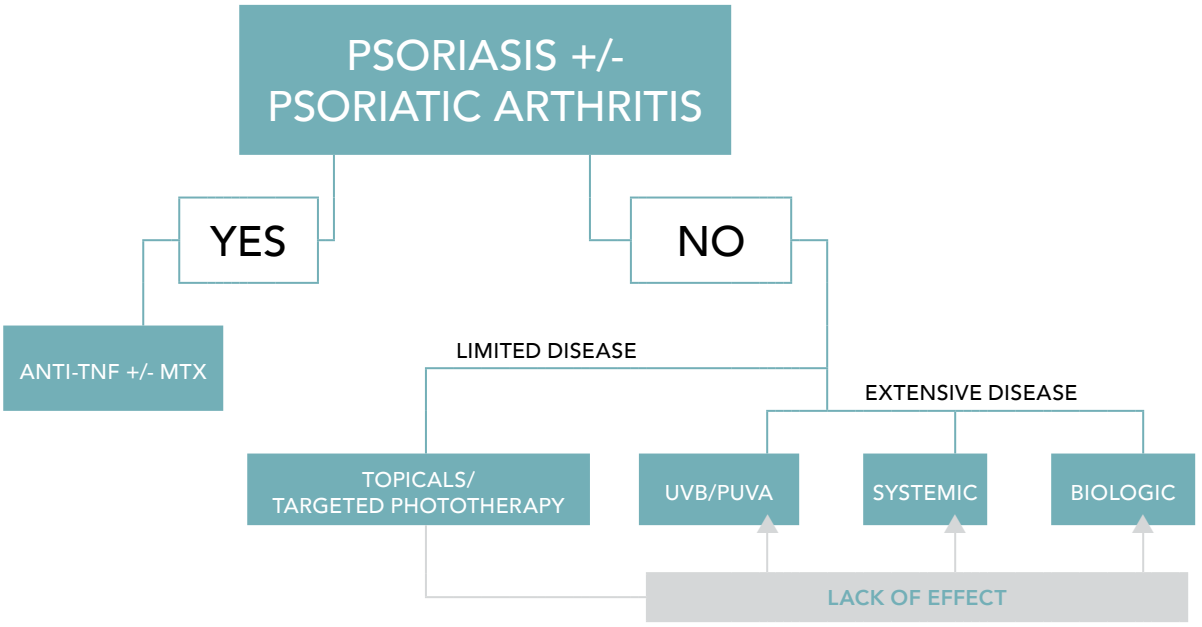
Nail disease has a prevalence of about 50 percent in those with psoriasis, though it has been said that 85 percent of psoriasis patients will have nail findings at some point in their lifetime.[4] Nail disease is not specific for psoriasis; it is also seen in alopecia areata and atopic dermatitis. Pits in the nails indicate nail matrix involvement. Numerous pits (> 10) on two nails is more suggestive of psoriasis. Oil spots are more specific for psoriasis. Nail bed involvement, which results in separation of plate from bed, gives the nails a yellowish discoloration. Nail disease is very difficult to treat and may be associated with psoriatic arthritis.

As shown in Exhibit 1, many distinct aspects of the immune system participate in the pathogenesis of this disease.[5] There are two major T cell-mediated pathways involved. These are Th1 where tumor necrosis factor (TNF) alpha is involved and Th17 where interleukin (IL)-23 and IL-17 are involved.

Exhibit 2 outlines the American Academy of Dermatology approach to treatment.[6] Mild psoriasis is treated with topical steroids, vitamin D agents, and keratolytics. Exhibit 3 summarizes the use of these three classes.[7] Moderate to severe psoriasis can be treated with phototherapy, oral systemic medications (methotrexate, apremilast, cyclosporine), and biologics. The severity of psoriasis is defined by the total body surface area (BSA) involved, and BSAs of < 3 percent, 3 percent to 10 percent, and > 10 percent are considered as mild, moderate, and severe disease, respectively.[8]

Methotrexate, an immunosuppressant, has been the backbone of therapy for moderate to severe psoriasis. It is used in combination with TNF inhibitors for psoriatic arthritis and can be used alone for moderate to severe psoriasis. At a median dose of 15mg per week, 36 percent of patients can achieve a 75 percent clearing of skin

Exhibit 2: American Academy of Dermatology Recommendations[6]



AAD = American Academy of Dermatology; TNF = tumor necrosis factor; MTX = methotrexate; UVB = ultraviolet B light; PUVA = psoralen plus ultraviolet light of A wavelength

(Psoriasis Area and Severity Index [PASI] 75) after 16 weeks of methotrexate monotherapy.[9] Treatment with methotrexate does require some laboratory monitoring in order to prevent adverse events. At baseline, a complete blood count, kidney function tests, liver function tests, and screens for hepatitis B and C and tuberculosis should be done. Patients with psoriasis are at higher risk of developing fatty liver disease, fibrosis, and cirrhosis from methotrexate than patients with other diseases commonly treated with methotrexate such as rheumatoid arthritis. Consideration for noninvasive evaluation for fibrosis with a test such as Fibroscan® should be given. Liver, blood, and kidney tests should be done monthly for the first three months of therapy and then every three to six months thereafter. To prevent adverse events, it is important that patients be educated that this agent is typically used once weekly rather than as a daily dose.

Apremilast is an oral phosphodiesterase-4 inhibitor that is orally administered. It is an immunomodulator that decreases pro-inflammatory cytokines (TNF-alpha, IL2, 12, 23) and increases anti-inflammatory ones (IL10). Apremilast is FDA-approved for both moderate to severe psoriasis and psoriatic arthritis. It is modestly effective with 33 percent of patients achieving a PASI 75 with this agent compared with a 5 percent response with placebo.[10]

Cyclosporine, an immunosuppressant, is now only used in selected cases. It is used in the crisis patient (erythrodermic psoriasis, very severe pustular psoriasis, or very severe plaque psoriasis), as a bridge to other long-term therapies with fewer adverse events such as biologics, and in pregnant women with severe flare without access to phototherapy or biologics. It has good efficacy and can produce clear or almost unblemished skin in 70 percent of patients in eight to 16 weeks at 5mg/kg/day. Cyclosporine should not be stopped abruptly or a disease flare can occur.

The biologics have revolutionized the treatment of moderate to severe psoriasis because they target the underlying pathophysiology of the disease. The American Academy of Dermatology (AAD) – National Psoriasis Foundation guidelines (NPF) recommend biologics as an option for first-line treatment of moderate to severe plaque psoriasis because of their efficacy and acceptable safety profiles.[11] Specifically, options include the inhibitors of TNF (etanercept, adalimumab, certolizumab, and infliximab), IL-12 and IL-13 (ustekinumab), IL-17 (secukinumab, ixekizumab, brodalumab), and IL-23 (guselkumab, tildrakizumab, risankizumab). Biologics that inhibit TNF, IL-12/23, and IL-17 are

Exhibit 3: Topical Treatments for Psoriasis[7]

Use and Efficacy	Limitations
Topical Corticosteroids (Class I to IV based on potency)	
Efficacy: Depends on class ***Amount and duration:*** For acute management, use twice daily until lesions are clear or almost clear. For proactive maintenance, apply topical corticosteroids, vitamin D analogue or topical calcineurin inhibitors twice/ week to clinically quiescent lesions (e.g., Monday & Thursday). Maximum dose for Class I use in adults, 50 g per week. ***Anatomical site:*** For sensitive body sites (face, axillae, inframammary and groin areas), use low-potency topical corticosteroids (Class VI or VII). For trunk and extremities, use Class I – III topical corticosteroids. ***Vehicle:*** For scalp, use solution or foam (Class I topical corticosteroids). Ointments are typically more effective than creams if same active ingredient is used, but ointments are generally not preferred due to greasiness.	With frequent and prolonged use of high-potency topical corticosteroids in normal-appearing skin or intertriginous areas, the following adverse events may occur; skin atrophy, telangiectasia, and striae. Regular examinations are recommended with long-term use. Systemic adverse events such as suppression of the hypothalamus pituitary and adrenal gland axis is rare and can be minimized by limiting long-term use of high-potency topical corticosteroids on large body surface areas – especially limiting such use in children.
Vitamin D Analogues (calcitriol; combination calcipotriene/calcipotriol)	
Efficacy Modest when used alone and relatively slow onset of action. In the same vehicle, calcipotriene and calcitriol are generally equally efficacious. ***Amount and duration:*** Use twice daily ***Maximum dose in adults:*** < 100g per week ***In children:*** < 50 g per week	The most common adverse events include skin irritation, burning, pruritus, and edema. Systemic absorption generally does not result in adverse outcomes unless patient has severe renal insufficiency. Calcipotriene may be inactivated by phototherapy – therefore apply after phototherapy.
Topical Calcineurin inhibitors – Tacrolimus 0.03%; pimecrolimus 1%	
Efficacy: Depending on the topical calcineurin inhibitor, they can be similar to Class VII to IV topical corticosteroids of calcipotriol. Tacrolimus 0.03% ointment and pimecrolimus 1% cream are used for face, axillary, and groin regions. ***Amount and duration:*** Use twice daily	Burning and pruritus may occur but typically lessens over time. Prior treatment with topical corticosteroids can reduce irritation. Topical calcineurin inhibitors have acceptable safety profiles, although boxed warning exists for risk of malignancy, no causal link has been identified with topical use in patients with psoriasis. Slower onset of action compared with topical corticosteroids.

(continued)

(continued)

Keratolytics	
Tazarotene	
Efficacy: Modest when used alone ***Amount and duration:*** Use once daily at night	Irritation and burning may occur. UV-B and tazarotene increase efficacy and reduce the dose needed for UV-B. Avoid in pregnancy
Salicylic Acid	
Efficacy: Unknown ***Amount and duration:*** Use 1 to 4 times daily ***Specific use:*** With topical corticosteroids to increase penetration (do not exceed Class III, IV and V topical corticosteroids), or with topical calcineurin inhibitors to increase penetration.	If applied to > 20% of the body surface area or used in combination with oral salicylates, systemic adverse events can rarely occur. Do not apply before phototherapy. Exercise caution in children.
Combination Topical Therapies	
Combined formulation: Topical corticosteroid and vitamin D analogue (e.g., calcipotriene/betamethasone dipropionate ointment or suspension/foam)	
Efficacy: High efficacy and longer remission than monotherapy with either topical corticosteroid or a vitamin D analogue. Also appropriate for proactive management for maintenance. ***Amount and duration:*** Use once daily. When clear or almost clear, use once a week.	Skin irritation occurs infrequently.

Exhibit 4: Choosing a Biologic for Psoriasis

TNF inhibitors great in:	IL-17 inhibitors great in:	IL-23 inhibitors great in:
• Psoriatic arthritis (peripheral and axial) • Pregnancy (certolizumab)	• Robust psoriasis efficacy • Psoriatic arthritis (peripheral and axial)	• Robust psoriasis efficacy • Few injections
Avoid TNF inhibitors in:	**Avoid IL-17 inhibitors:**	**Avoid IL-23 inhibitors:**
• Demyelinating disease • Hepatitis B	• Personal history of inflammatory bowel disease	• Psoriatic arthritis involving spine
TNF inhibitors not preferred:		
• History of latent tuberculosis • Advanced heart failure		

also approved for the treatment of psoriatic arthritis.

Laboratory monitoring recommendations from the AAD–NPF guidelines are similar to those for methotrexate. Baseline testing should include complete blood counts, complete metabolic profiles, and hepatitis B and C and tuberculosis screening. The only ongoing recommended monitoring is a tuberculosis screening yearly. Ongoing complete blood count and complete metabolic profile are not supported by evidence and are to be assessed at the discretion of the provider.[11]

Selecting a biologic should be based on efficacy, safety, convenience to patient, patient preference based on shared decision-making, and cost. In terms of efficacy, a 2020 meta-analysis of PASI outcomes found that brodalumab, guselkumab, ixekizumab, and risankizumab were associated with the highest PASI response rates in both short-term and long-term therapy.[12] This analysis found that the number needed to treat (NNT) to achieve a PASI 75 was 1.19 for risankizumab compared to 2.87 for etanercept and 3.92 for apremilast; the NNT to achieve PASI 100 (clear skin) are higher for all agents available to treat moderate to severe psoriasis, but follow the same pattern. Exhibit 4 shows some other issues to consider in selecting biologics.

Conclusion

Biologic agents have changed the treatment paradigm in psoriasis, offering long-term safety and efficacy to those with moderate to severe disease. They are an option for first-line treatment of moderate to severe plaque psoriasis. The IL-17 and IL-23 inhibitors are the most efficacious in terms of PASI response rates and NNT to achieve a PASI 75 and PASI 100.

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Current Updates and Advances in Diagnosis and Treatment of Spinal Muscular Atrophy

Julie A. Parsons, MD

For a CME/CEU version of this article please go to
http://www.namcp.org/cmeonline.htm, and then click the activity title.

Summary

Spinal muscular atrophy (SMA) is a devastating neuromuscular disorder. It is currently a very exciting time for clinicians, patients, and parents for treating this disorder because a new gene therapy and other treatments are altering the natural course of the disease.

Key Points

- Nusinersen and risdiplam are effective for all types of SMA.
- Onasemnogene abeparvovec-xioi, gene replacement therapy, is effective for Type I SMA.
- Efficacy is improved when treatment is initiated soon after diagnosis.

SPINAL MUSCULAR ATROPHY (SMA) IS a clinically and genetically heterogeneous group of diseases in which there is a loss of anterior horn cells and progressive muscle atrophy without involvement of the corticospinal tract. Progressive symmetrical muscle weakness and atrophy occur because of loss of lower motor neurons in the spinal cord and brainstem nuclei. Poor weight gain with growth failure, restrictive lung disease, scoliosis, and joint contractures are common complications of untreated SMA. Death results primarily from respiratory failure.

The cause of the most usual form of SMA is inactivating mutations of the survival of motor neuron 1 (SMN1) gene which was identified in 1995. The most common mutation of SMN1 is on the 5Q chromosome and thus the disease is call SMA5Q or SMN1-related SMA.[1] SMN1-related SMA is an autosomal recessive neuromuscular disease caused by homozygous deletion or pathogenic variant in the survival of the SMN1 gene and for the rest of this article will be referred to as SMA. It has an incidence of one in 10,000 live births. Carrier frequency is one in 40 to one in 60, which is similar to cystic fibrosis. It is a pan-ethnic disorder.

In SMA, the affected person has a non-functional SMN1 gene which normally produces 90 percent of the SMN protein.[2] They still have a functional SMN2 gene, a back-up gene which produces some low amounts of SMN protein. In humans, SMA disease severity correlates with the number of copies of the SMN2 gene and the level of functional protein produced. Those with one or two copies of the gene have SMA Type 1, the most severe form.[3] Those with two to three copies have SMA Type 2, and those with four copies have SMA Type 3. People with five or more copies of SMN2 are clinically unaffected, even though they have non-functioning SMN1. SMA is diagnosed based on genetic testing to identify non-functional SMN1 and the number of SMA2 gene copies.

Genetic testing is important in neuromuscular disease to establish diagnosis, help with disease management, and inform family members of their own risk (Exhibit 1).[4] The American College of Gynecology recommended in 2017 that all women be offered prenatal carrier testing for SMA. In July of 2017, Missouri was the first state to pass legislation adding SMA to their newborn screening panel. Newborn screening for SMA was added to the Federal Recommended Uniform Screening Panel in 2018. As of 2021, all but 13 states have added SMA to their screening panels.[5] Genetic testing is widely available, but the turnaround time should be

Exhibit 1: Importance of Genetic Testing for Neuromuscular Diseases[4]

Help establish a diagnosis	• Shorten diagnostic odyssey – rule out other diseases, confirm suspected diagnosis. • Alleviate the need for invasive and painful procedures such as muscle biopsy. • Improve the psychological impact on patients and family members by confirming the diagnosis. • Mitigate costs by preventing unnecessary procedures and treatments.
Help with disease management	• Provide a prognosis – i.e., indicate expected severity of disease. • Identify patients eligible for treatments. • Guide treatment plan. • Identify patients eligible for clinical trials.
Effects on family members	• Guide the testing of relatives • Assist with decisions regarding family planning

Exhibit 2: Classification System for Spinal Muscular Atrophy[6]

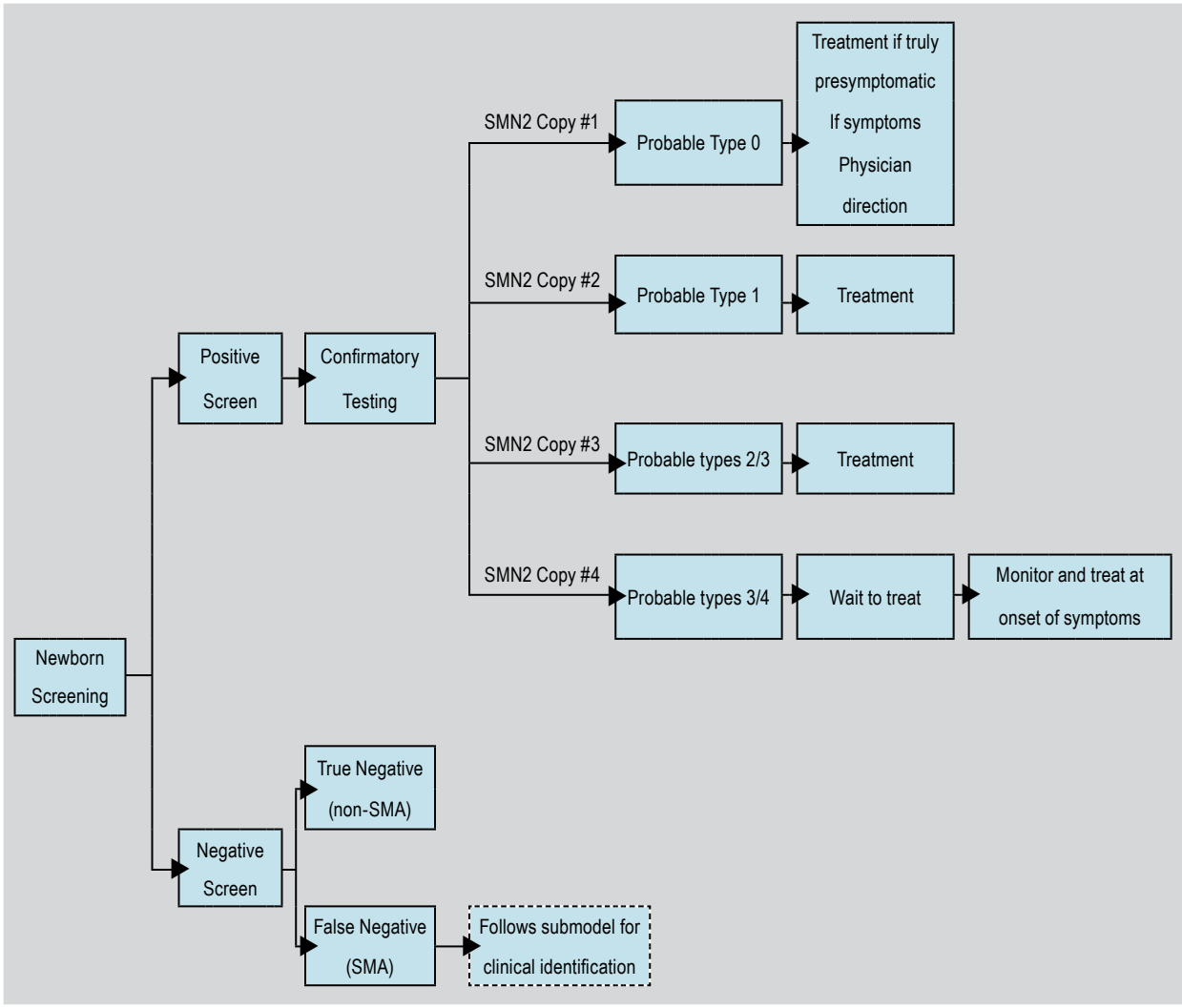
Type	Age of Onset	Highest Motor Activity	Natural Age of Death
0	Prenatal	Respiratory support	< 1 month
1	0 to 6 months	Never sits	< 2 years
2	< 18 months	Sits, does not stand alone	Adult
3	> 18 months	Stands alone, walks unassisted	Adult
4	> 21 years	Walk during adulthood unassisted	Adult

short and SMN copy numbers should be included in the report. Free testing is available through Invitae Corporation (sponsored by Biogen) for patients suspected or clinically diagnosed with SMA.

Those with SMA are classified based on function as non-sitters, sitters, and walkers (Exhibit 2).[6] Type 1 comprises approximately 60 percent of cases, Type 2 30 percent, and Type 3 10 percent. Without treatment, only 8 percent of patients with Type 1 survive to 20 months of age.[7,8] Patients with more severe disease require a significant amount of supportive care and equipment; this can include power chairs, walkers, constant noninvasive ventilation, and cough assist devices.

There are consensus guidelines on managing these patients.[9,10] Improved standards of care, especially for nutrition and aggressive pulmonary care, have dramatically improved the survival of those with SMA Type I, even without specific treatments that alter the underlying pathology.[11,12] The prolongation of survival from improved care does not impact achievement of motor milestones; thus, non-sitters will never become sitters with improved standards of care.

Exhibit 3: Proposed Treatment Protocol plus SMA Newborn Screen[24]



The mechanistic strategies to treat SMA are aimed at increasing SMN, muscle activation, which is SMN independent, neuroprotection of the motor neurons affected by loss of SMN protein, and muscle protection to prevent or restore the loss of muscle function in SMA. The SMN strategies currently marketed include improving production of functional SMN protein by modification of SMN2 mRNA splicing and gene replacement.[13] Nusinersen (Spinraza®) was the first FDA-approved therapy for SMA, and it targets SMA2 splicing modification. Risdiplam (Evrysdi®), approved in 2020, is also a SMA2 splicing modifier. Gene replacement is replacement of the faulty SMN1 gene using viral-vector-based gene therapy. Onasemnogene abeparvovec-xioi (Zolgensma®) is the FDA-approved gene replacement product.

Nusinersen, an antisense oligonucleotide, increases the amount of SMN protein that is produced. It has been studied in infantile onset SMA, later onset SMA, and presymptomatic SMA. The trials of SMA therapies all use survival, need for ventilation assistance, and measures of motor function to assess efficacy. In a randomized, double-blind, sham-controlled study of nusinersen in 121 infants (≤ 7 months) with SMA Type I, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (37 of 73 infants [51%] versus 0 of 37 [0%]), and the likelihood of event-free survival was higher in the nusinersen group than in the control group (hazard ratio for death or the use

of permanent assisted ventilation, 0.53; $p = 0.005$).[14] In a multicenter, double-blind, sham-controlled study in 126 patients with later-onset SMA (2 to 12 years), 57 percent of the children in the nusinersen group, as compared with 26 percent in the control group, had an increase from baseline to month 15 in the Hammersmith Functional Motor Scale-Expanded (HFMSE) score of at least three points ($p < 0.001$), and the overall incidence of adverse events was similar in the nusinersen group and the control group (93% and 100%, respectively).[15] Long-term results from the later onset cohorts found benefit out to three years with continued therapy.[16] The pre-symptomatic study was an open-label, single-arm trial of nusinersen in infants with genetically diagnosed SMA (mostly less than or equal to 1 month at enrollment). At the end of this trial, the 25 children were a median 34.8 months of age and past the expected age of symptom onset for SMA Types I or II; all were alive and none required tracheostomy or permanent ventilation.[17] Four (16%) participants with two SMN2 copies utilized respiratory support for six hours per day or more for seven consecutive days or more that was initiated during acute, reversible illnesses. All 25 participants achieved the ability to sit without support, 23 of 25 (92%) achieved walking with assistance, and 22 of 25 (88%) achieved walking independently. Overall, 88 percent of the participants were able to maintain full oral feeds. Nusinersen demonstrated durability of effect, with a median 2.9 years of follow up.

An analysis from the pre-symptomatic trial examining long-term swallowing data was presented at the 2021 Virtual SMA Conference. Ninety-two percent of patients who initiated nusinersen treatment as pre-symptomatic infants maintained the ability to swallow after a median of 3.8 years.[18] This is in contrast with the natural history of SMA where impaired swallowing is expected for people with two or three SMN2 copies and can lead to an increased risk of aspiration pneumonia, choking, and failure to thrive. Additionally, all participants with three SMN2 copies and 73 percent with two SMN2 copies were reported by their caregiver as being fed exclusively by mouth.

Nusinersen is given by intrathecal bolus injection which requires a spinal tap for each dose. This agent has a long half-life (several months) in the central nervous system tissue, but dosing is required relatively frequently to keep the drug levels up. Initially loading doses to saturate motor neurons are given four times over three months. Maintenance doses to maintain effective drug levels are then given every four months. It does take time to see positive motor function benefits (~15 months of treatment). The motor benefits may include the ability to sit or walk, the ability to feed orally, and the ability to operate a power chair, write, and feed themselves. These are striking benefits compared to the natural history for Type 1. Declines in function in the placebo groups of the nusinersen trials illustrate the importance of starting therapy early in the disease process. The greatest improvements in motor milestone scores were observed in infants treated with nusinersen in the presymptomatic stage of SMA; thus, the earlier treatment can begin, the better the outcomes.[17] Nusinersen appears to be well tolerated by the patients with no major adverse events different from placebo. Nusinersen is FDA-approved for treatment of SMA in pediatric and adult patients with SMN1-related SMA. Nusinersen costs $125,000 per dose, which makes the first-year cost of the drug alone $750,000 and that does not include the administration costs. Subsequent years cost $382,000 for the drug alone.

Risdiplam is an oral SMN2 splicing modifier recently FDA-approved (2020) for the treatment of SMA in adults and children two months and older. Risdiplam is designed to increase and sustain SMN protein levels both throughout the central nervous system and peripheral tissues of the body. It has been studied in infants with Type 1 SMA and in children and young adults (2 to 25 years old) with Type 2 or 3 SMA and increases SMN levels about twofold. In addition to the studies included in the FDA submission, risdiplam is being studied in a broad clinical trial program in SMA, with patients ranging from newborns to 60 years old, and includes patients previously treated with other SMA therapies.

In a Phase II/III, open-label study of risdiplam in 21 infants one to seven months of age who had type 1 spinal muscular atrophy, four infants were in a low-dose cohort and were treated with a final dose at month 12 of 0.08 mg of risdiplam per kilogram of body weight per day, and 17 were in a high-dose cohort and were treated with a final dose at month 12 of 0.2 mg per kilogram per day.[19] The baseline median SMN protein concentrations in blood were 1.31 ng per milliliter in the low-dose cohort and 2.54 ng per milliliter in the high-dose cohort; at 12 months, the median values increased to 3.05 ng per milliliter and 5.66 ng per milliliter, respectively, which represented a median of 3.0 times and 1.9 times the baseline values in the low-dose and high-dose cohorts, respectively. Serious adverse events included pneumonia, respiratory tract infection, and acute respiratory failure. At the time of this publication, four infants had died of respiratory complications. Seven infants in the high-dose cohort and no infants in the low-dose cohort were able to

sit without support for at least five seconds. Ninety percent of infants were event free after receiving risdiplam for 12 months (event free was defined as alive with no permanent ventilation). The higher dose of risdiplam (0.2 mg per kilogram per day) was selected for Part II of the study which has not yet been published and is the FDA-approved dose for those two months to two years of age.

Risdiplam has two major advantages – it is orally administered, at home, rather than requiring an intrathecal injection, and it has a lower cost. Risdiplam is priced based on patient weight. For an infant under 15 pounds – usually two years of age – the annual price checks in at less than $100,000, and it is capped at $340,000 per year, or 44 pounds, normally around the weight of a six-year-old.[20] Whether this will become the predominant SMN2 splice modifier may depend on long-term data with each agent.

Gene transfer therapy was the next iteration in SMA therapy. This therapy is designed to deliver a fully functional human SMN gene into target motor neuron cells, leading to production of sufficient levels of SMN protein required to improve motor neuron function. This therapy leads to a rapid onset of effect in addition to sustained SMN protein expression. Within a day of infusion, the SMN levels begin to increase.

Onasemnogene abeparvovec-xioi, the FDA-approved agent, crosses the blood-brain barrier and targets neurons. It is non-integrating, has a rapid onset of effect, remains stable within the nucleus, and produces sustained SMN expression. Its FDA-approved indication is treatment of pediatric patients less than two years of age with SMA with biallelic mutations in the SMN1 gene. In the clinical trial that led to approval (START), all 15 patients treated with a single infusion were alive and event-free at 20 months of age, as compared with a rate of survival of 8 percent in a historical cohort.[21] As of June 11, 2020, all patients (100%) were alive and free of permanent ventilation. The mean age of patients was 5.2 years and the mean time since gene therapy treatment was 5.0 years. In the high-dose cohort (12 subjects, 2.0×10^{14} vg per kilogram), a rapid increase from baseline in the score on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scale followed gene delivery, with an increase of 9.8 points at one month and 15.4 points at three months, as compared with a decline in this score in a historical cohort. Of the 12 patients who had received the high dose, 11 sat unassisted, nine rolled over, 11 fed orally and could speak, and two walked independently. Elevated serum aminotransferase levels occurred in four patients and were attenuated by prednisolone.

In an open-label, single-arm, single-dose, Phase III trial [STR1VE] in 22 infants (< 6 months) and have spinal muscular atrophy with biallelic SMN1 mutations (deletion or point mutations) and one or two copies of SMN2, gene therapy resulted in 13 of 22 patients achieving functional independent sitting for 30 seconds or longer at the 18 month of age study visit (versus 0 of 23 patients in the untreated Pediatric Neuromuscular Clinical Research (PNCR) dataset cohort; $p < 0{\cdot}0001$).[22] Twenty patients (91%) survived free from permanent ventilation at age 14 months (versus 6 [26%], $p<0{\cdot}0001$ in the untreated PNCR cohort). Patients maintained ability to thrive and achieve motor milestones. There was a rapid and sustained improvement in motor function after dosing.

In contrast to the natural history of SMA, children treated with Zolgensma pre-symptomatically in the Phase III SPR1NT trial achieved age-appropriate motor milestones within the World Health Organization (WHO) window of normal development (e.g., sitting, standing, and walking) were able to eat exclusively by mouth and did not require ventilatory support of any kind. All patients from this trial were alive and free of ventilatory support of any kind in the most recent data update. All patients fed orally and did not require feeding tube support of any kind.

There is an ongoing trial of this gene therapy in children between six and 60 months who have three copies of SMN2 and can sit alone for 10 seconds or more, but cannot stand or walk. Interim data reports from this trial showed clinically meaningful changes in motor function occurred in these older patients. This trial is temporarily on hold while issues of inflammation in animal studies is under investigation.

This gene therapy is given as a single intravenous weight-based infusion. Systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) must be given for one day before infusion and continued for a total of 30 days after administration to dampen or circumvent the expected immune response to the adeno-associated virus viral capsid in the host liver cells. This therapy costs $2.1 million along with additional related medical and pharmacy costs of hospitalization for receiving the therapy and follow-up medications and laboratory monitoring and clinical care.

Identification of homozygous deletion of SMN1 combined with three or fewer SMN2 gene copies is a powerful predictor of disease and identifies the groups (Type 1 and Type 2) who would benefit substantially from the new and emerging

therapies.[23,24] There is strong evidence that the irreversible loss of motor neurons in humans with SMA Type 1 begins early in the perinatal period, with severe denervation in the first three months and loss of more than 90 percent of motor units within six months of age. Patients dosed early in age (less than three months) can achieve the ability to stand or walk. Nusinersen, risdiplam, and onasemnogene abeparvovec-xioi results suggest that dosing early in life will yield the best outcomes in infants with SMA1, thus early diagnosis and therapy should be encouraged.

A proposed treatment protocol is shown in Exhibit 3.[24] All clinicians agree on treating those with three or fewer SMN1 gene copies, but treatment of those with four copies of the SMN1 gene while asymptomatic is controversial. A multidisciplinary team for clinical care is key to managing those with SMA whether treated with the new therapies or not.

Conclusion

Novel therapies are now available for treatment of SMA. Early diagnosis is important in order to start preliminary treatment because earlier treatment leads to better patient outcomes. Newborn screening programs in each state are key to successful early intervention. Long-term follow-up with these new treatments is important in order to understand the changing phenotypes of this disease.

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Recent Developments in the Treatment of Major Depressive Disorder: Overcoming Barriers through Personalized Care

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For a CME/CEU version of this article, please go to
http://www.namcp.org/home/education, and then click the activity title.

Summary

Outcomes in the management of major depressive disorder can be improved through personalized care. This may involve improvement in the systems of care and a standardized approach to choosing and monitoring therapy. Using pharmacogenomics to select therapy is becoming more common. Lastly, there are now treatment options for treatment-resistant depression.

Key Points

- Routine depression screening and incorporating proven strategies to help individualize care can improve outcomes.
- Antidepressant medications and psychotherapy, singly and in combination, are the standard of care for most depressed outpatients.
- There are many safe and effective options for multiple lines of therapy.
- Improving methods to match patients with specific drugs can further personalize care and improve outcomes.
- Novel therapies provide additional options for patients with treatment resistance.

DEPRESSION IS ONE OF THE WORLD'S greatest public health problems. Major depressive disorder (MDD) has a point prevalence of about 8 percent in the United States (U.S.).[1] Bipolar disorder has a 3 percent point prevalence. Together, these disorders have a 20 percent lifetime prevalence. MDD is the greatest cause of workplace disability, and bipolar disorder is the eighth greatest cause of disability. As economic circumstances improve, depression rates in industrially developed countries actually increase. Mood disorders are highly comorbid and amplify the burden of co-occurring conditions. At least three-quarters of those who die by suicide have a depressive disorder.[2]

The diagnosis of mood disorders has evolved over time. Prior to the 1970s, diagnoses were based on brief stereotypic descriptions tied to theories of the mind (i.e., "neurotic depression") and studies documented poor reliability. More than a decade of research led to the atheoretical/standardized/specified approach introduced in the American Psychiatric Association (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM)-III in 1980 which was heralded as paradigm changing. The APA established an ongoing, iterative process for making updates to the diagnostic criteria. The DSM-IV was published in 1994 and DSM-V in 2013. Despite refinements, the basic criteria for a MDD have not changed in 40 years; reliability actually decreased in DSM-V field trials.

There are several limitations in current approaches to diagnosis of depressive disorders. The clinical presentations of people meeting criteria for MDD are quite heterogeneous (Exhibit 1).[3] Given the associations between signs and symptoms and underlying neurobiological processes, these conditions are also likely to be heterogeneous in terms of pathophysiology. Some common and important symptoms, including irritability, pain, and anxiety, are not included in the diagnostic criteria.

Exhibit 1: Heterogeneity of Key Depressive Symptoms[3]

- **Psychological/emotional (Required symptoms)**
  - Depressed mood (blue, down, sad, hopeless or empty/drained)
  - Anhedonia and/or diminished libido
- **Psychological/emotional**
  - Guilty ruminations, decreased self-esteem or worthlessness
  - Suicidal ideations and behavior
- **Physical**
  - Sleep (insomnia or hypersomnia)
  - Appetite (loss of appetite/weight loss or hyperphagia/bingeing/weight gain)
- **Cognitive**
  - Poor concentration and memory issues, reduced abstraction, indecision
  - Psychomotor retardation

Co-occurring conditions commonly complicate the clinical course and can adversely affect treatment response.

The U.S. Preventive Services Task Force recommends depression screening for adults in all primary care settings with a validated tool.[4] This improves the identification of depression and, when combined with adequate clinical support, improves clinical outcomes. Importantly, for screen-positive adults, there must be a link between screening and intervention (antidepressants, psychotherapy, or both) to ensure engagement of the patient and delivery of care. Guideline-concordant treatment has been shown to improve outcomes. For screen-positive pregnant and postpartum women, psychotherapy is preferred over pharmacotherapy. Overall, depression screening is inexpensive and has little associated risk.

Mild-to-moderately severe episodes respond equally well to antidepressant medications or focused, time-limited psychotherapies. Patient preference, motivation for change, and adherence influence outcomes for either type of therapy. Access to psychotherapy is not readily available in some settings. When effective, time-to-benefit favors antidepressants over psychotherapy. Pharmacotherapy becomes relatively more important when severity is very high and/or there is urgency because of disability or impairment. Combined pharmacotherapy and psychotherapy has additive benefits for patients with more chronic, severe, or complicated illnesses. A large body of research indicates that nonspecific elements of care account for a large proportion of the benefit of treatment.

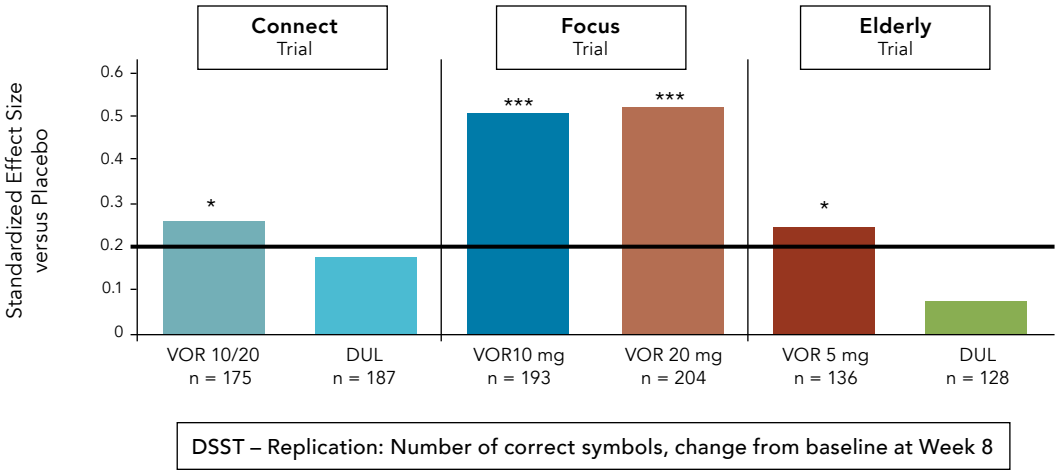
Improving delivery of care improves outcomes. Over the past 20 years, three strategies have been developed to help to individualize care and improve treatment outcomes:

- measurement-based care (MBC)
- collaborative care
- shared decision-making

MBC consists of several simple components – accurately assessing symptom severity, ensuring adequate antidepressant dosage, assessing tolerability of medication, and monitoring and promoting treatment adherence.[5] Quick and easy to use, empirically validated assessments are available to monitor symptom severity and adverse events. The preferred symptom scales are Patient Health Questionnaire 9 item (PHQ9) or Quick Inventory of Depressive Symptomatology-Self-Rated (QIDS-SR). MBC has been shown to result in better symptom and functional scores compared to usual care.[6]

Collaborative care models incorporate elements of MBC to improve accuracy in monitoring of symptoms and adverse events. There is involvement of nurses and other professionals to increase clinical contact and therapeutic support and ensure timely progression through algorithms. Availability of psychologists and other clinicians provides

Exhibit 2: Vortioxetine Therapy Improves DSST Performance in Three Clinical Trials of MDD[9-11]



*$p < 0.05$, ***$p < 0.001$

DSST = digit symbol substitution test; VOR = vortioxetine; DUL = duloxetine

empirically validated psychotherapies.[5] Collaborative care has been shown to improve response to therapy and satisfaction with care.[7]

Shared decision-making (SDM) is collaborative and moves away from paternalism. It allows patients and their providers to make decisions together, taking into account both the best scientific evidence and the patient's values and preferences. SDM fosters respect of the provider's expert knowledge and the patient's right to be fully informed of all care options and their potential harms and benefits. SDM provides patients with support to make the best individualized care decisions and enables providers to feel more confident that the treatments they prescribe will be helpful for their patients.

Consensus across guidelines is that antidepressants for first-line use are the selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs, bupropion), and noradrenergic and specific serotonergic antidepressant (NaSSA, mirtazapine). Mirtazapine is often reserved for older patients. Antidepressants are largely chosen on the basis of provider beliefs and habits, cost, perceived tolerability and effectiveness, and ease of prescription.

Three newer brand name options are available for switches in case of failures and usually require prior authorization Vilazodone is a SSRI, plus is a potent serotonin 1a partial agonist.[8] It causes a lower incidence of sexual adverse events than older antidepressants but requires titration to optimal dose. Levomilnacipran is a SNRI that is the stereoisomer of milnacipran (approved for fibromyalgia). It is relatively more potent for norepinephrine uptake than other SNRIs and has a wide therapeutic range of doses (40 to 120 mg/day). Vortioxetine is a SSRI with a range of other effects on serotonin receptors and a wide therapeutic range of doses (5 to 20 mg/day). It causes a lower incidence of sexual adverse events than other SSRIs and may have greater pro-cognitive effects than other antidepressants. As shown in Exhibit 2, vortioxetine improves performance on the digit symbol substitution test (DSST), which measures executive functioning, working memory, attention, and speed of processing.[9-11] The effect of vortioxetine on DSST performance is not mediated solely through an improvement in general depressive symptoms.

Even today with numerous available antidepressants, there are significant unmet needs. There is limited specific efficacy of all the first- and second-line antidepressants. They are only 10 to 20 percent better than placebo in randomized clinical trials. Intolerable adverse events occur in about 10 percent of patients. Most of the antidepressants have inconsistent effects on key symptoms of insomnia and anxiety, resulting in a need for additional

Exhibit 3: Antidepressant Therapy Follows an Implicit Algorithm: *From Simpler to More Complex*

- **First-Line:** Begin with an adequate trial of a first-line antidepressant (usually a generic formulation of an SSRI or SNRI)
- **Second-Line:** Switch to another first-line antidepressant (some favor switching to a different type of medication, e.g., mirtazapine)
- **Third-Line:** Patented antidepressants, combination and adjunctive strategies, or older antidepressants (i.e., TCAs or MAOIs)
- **Fourth-Line:** Neuromodulation strategies (TMS or ECT), ketamine infusions, or intranasal esketamine
- **Fifth-Line:** VNS or unproven or experimental strategies

ECT = electroconvulsive therapy; MAOI = monoamine oxidase inhibitor; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TMS = transcranial magnetic stimulation; VNS = vagus nerve stimulation.

medications to treat these symptoms. They have a relatively slow onset of action. There is no reliable method to optimize matching of antidepressants to particular patients. Approximately 20 to 30 percent of treated patients have treatment-resistant depression (TRD). As all first- and second-line therapies target monoamine systems, patients with TRD may need treatments that target new mechanisms of action.[12]

As shown in Exhibit 3, antidepressant therapy typically follows an implicit algorithm. A decision must be made if the first-line choice fails. Parsimony favors switching (i.e., do ONE thing well), but adjuncts are easier to implement (i.e., avoids washout and cross-titration). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial did not answer this question definitively, but appeared to favor adjunctive strategies.[13] STAR*D clinicians only favored switching when the index antidepressant was poorly tolerated.

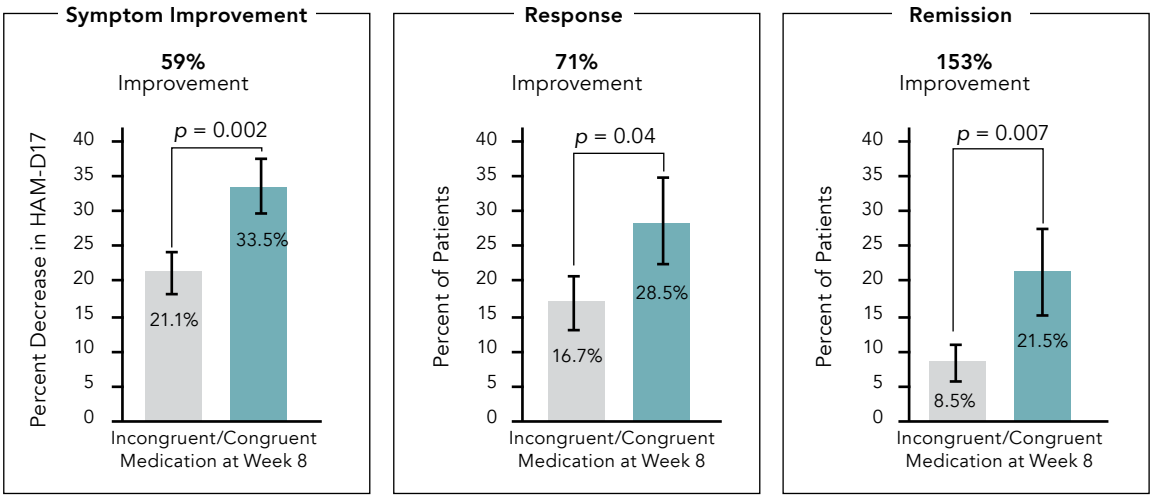
One way to improved medication selection for second-line therapies may be pharmacogenomic testing. At least eight genes have alleles that are associated with poorer tolerability or nonresponse to one or more antidepressants. Most of these genes affect enzymatic metabolism (CYP isoenzymes) and others determine the activity of the serotonin transporter, conversion of dietary folic acid to methylfolate, or blood-brain transport. Drug-gene interactions are more common for individuals who are homozygous for affected alleles and can be amplified by interactions with other drugs. Specific drug-gene interactions are uncommon and explain less than 1 percent of outcome variance. Combinatorial pharmacogenomic testing may improve drug selection and increase response rates by 10 percent.[14] At least from one trial, the primary value of pharmacogenomic testing is avoiding use of medications that are more likely to cause adverse effects.[15] In this trial, genomic testing that suggested a particular agent be used with increased caution and with more frequent monitoring was labeled as incongruent. Patients taking incongruent medications prior to baseline, who switched to congruent medications, experienced greater symptom improvement, response, and remission by week eight compared to those remaining incongruent (Exhibit 4).[15]

Typical third-line options when there is a lack of response are a switch to one of the newest antidepressants, use combination and adjunctive strategies, or choose an older antidepressant (tricyclic or monoamine oxidase inhibitor). By current convention, an adjunct is added to an antidepressant when there has been a suboptimal response. The FDA defines augmentation when the second medication enhances the mechanistic action of the first.

Combination strategies are typically two antidepressants that work on different monoamine systems. Selectivity and safety of newer generation antidepressants have made combining antidepressant medications an appropriate therapeutic choice. Bupropion and mirtazapine are the preferred agents for use in combined therapy. No antidepressant has FDA approval for this use, and only mirtazapine is supported by positive, well-controlled studies.[16,17] Routinely combining antidepressants has not been shown to improve outcomes, but dosing may not have been sufficient in the available clinical trials.[18,19]

Older adjunctive strategies include adding a benzodiazepine, hypnotic, buspirone, psychostimulant, lithium or other mood stabilizer, thyroid hormone (usually triiodothyronine [T3]), or first-generation antipsychotic to an antidepressant. Adjunctive therapy with second-generation antipsychotics is the most widely

Exhibit 4: Value of Pharmacogenomic Testing[15]



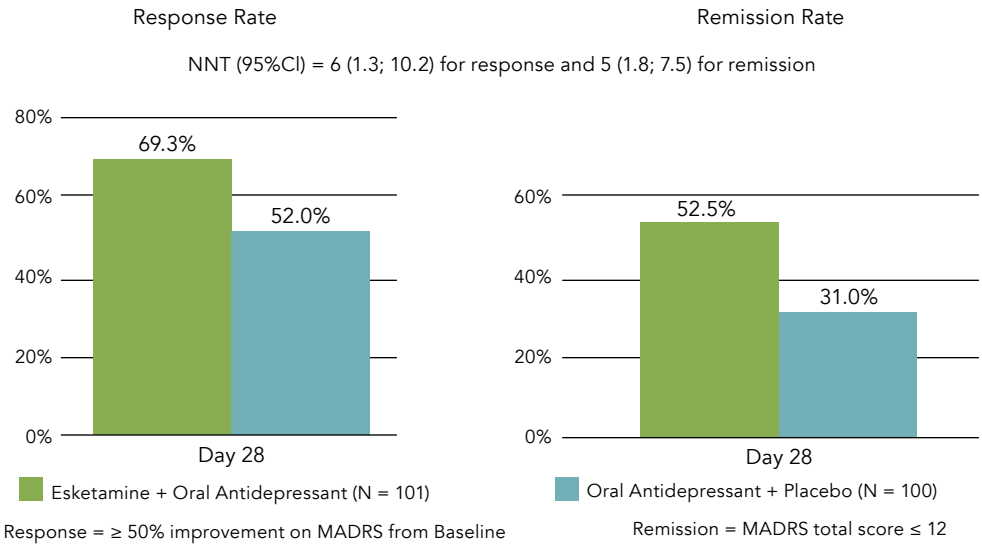
studied and commonly used adjunctive strategy for MDD and is the treatment of first choice for psychotic depressions.[20,21] For TRD, quetiapine, aripiprazole, and brexpiprazole are FDA-approved, as is olanzapine plus fluoxetine. There are also positive studies for risperidone. The relative efficacy of various agents and optimal duration of therapy are not established. Cost-effectiveness of this strategy is unlikely, but not adequately studied. There are long-term safety concerns, including metabolic complications and tardive dyskinesia, which should be monitored.

Other options for TRD include neuromodulation strategies (transcranial magnetic stimulation [TMS] or electroconvulsive therapy [ECT]), ketamine infusions, or intranasal esketamine. When all of these have failed, vagal nerve stimulation (VNS) or unproven or experimental strategies are the only options left.

Ketamine, an anesthetic agent that has been shown to block N-methyl-D-aspartate (NMDA) receptors, been used intravenously to treat TRD, chronic pain, post-traumatic stress disorder, and other conditions. The theory of the efficacy of ketamine involves provoking release of glutamate which then interacts with other receptors beyond the blocked NMDA receptor. At higher concentrations, ketamine is also a Mu opioid agonist which appears to cause a release of endogenous opioids and neurotransmitters such as norepinephrine and dopamine. In seven trials encompassing 147 participants, ketamine produced a rapid, yet transient, antidepressant effect, with odds ratios for response and transient remission of symptoms at 24 hours equaling 9.87 (4.37 to 22.29) and 14.47 (2.67 to 78.49), respectively, accompanied by brief psychotomimetic and dissociative effects.[22] The effective dose is approximately 0.5 mg/kg infused over 40 min two to three times per week, and the antidepressant effect is typically evident within three doses. The antidepressant activity is largely unrelated to dissociative effects. This treatment is generally not covered by insurance, and there are residual concerns about tolerance and longer-term safety. There is increasing evidence of sustained benefit with weekly doses for months or years.

Intranasal esketamine (Spravato®) is the first drug to target NMDA receptors to be FDA-approved as an adjunctive therapy for TRD. This product is the more potent stereoisomer of racemic ketamine with an intranasal delivery for physician and patient convenience. The 84 mg intranasal dose is approximately equivalent to 0.5 mg/kg of racemic ketamine. The retail cost is about $800 per dose, and this agent must be administered by a health care provider with a period of observation post-dose. Insurance coverage has been increasing for this treatment. This agent in combination with antidepressants improves response and remission rates compared to antidepressants alone (Exhibit 5).[23] It can also reduce risk of relapse when continued with a dose every one to two weeks after response. Continued esketamine and antidepressant

Exhibit 5: Intranasal Esketamine Plus Oral Antidepressant* versus Active Control in Treatment-Resistant Depression[23]



*escitalopram, sertraline, venlafaxine ER or duloxetine

treatment decreased the risk of relapse by 51 percent among patients who achieved stable remission while treated with the combination and 70 percent among those who achieved stable response compared with antidepressant and placebo treatment.[24]

There are some unresolved concerns and issues with esketamine. Some experts have questioned whether R-ketamine (the other enantiomer) is the more effective stereoisomer for treatment of depression. Predictors of outcomes to maximize benefit and methods for transition to other therapies for relapse prevention are needed. Innovations are needed to improve efficiency of administration as a means to reduce the cost of treatment; currently, the medication must be administered under supervision. Self-administration has been used in the relapse prevention trials, but is not allowed under current FDA approval. Better longer-term safety data and proof that abuse is not occurring will likely be needed before any changes in the FDA approval will happen.

Conclusion

The lives of depressed patients can be improved by routine screening and incorporating proven strategies to better individualize care. Antidepressant medications and psychotherapy, singly and in combination, are the standard of care for most depressed outpatients. There are many safe and effective options for three lines of therapy. Improving methods to match patients with specific drugs can further personalize care and improve outcomes. Novel therapies that target non-monoaminergic neuronal systems, such as esketamine, provide additional options for patients with TRD.

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Novel Treatment Advances and Approaches in the Management of Relapsed/Refractory Multiple Myeloma: Expert Strategies on the Role of Emerging Therapies

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Summary

Despite advances in treatment, multiple myeloma remains an incurable disease and relapses occur commonly. There are now numerous treatment options for Relapsed/Refractory Multiple Myeloma (RRMM) with more on the way. Triple therapy is now the norm for treatment.

Key Points

- Triple therapy should be used for most patients.
- For early relapse, daratumumab should be considered as part of the regimen.
- The most important factor in choosing a regimen is that it produces stable disease or better and is well tolerated.

MULTIPLE MYELOMA (MM) IS THE second most common hematologic malignancy in the United States (U.S.) with about 10,000 new cases diagnosed annually. With improvements in therapy, patients are living longer with this disease. There are an estimated 150,000 people living with MM in the U.S.

The goal of treating newly diagnosed MM in stem cell transplant eligible and ineligible patients is to gain the best depth of response by using an effective induction regimen followed by consolidating the response with a transplant or medication and offering maintenance strategies to prolong the first progression-free survival (PFS1) benefit. The combination of lenalidomide, bortezomib, and dexamethasone (RVD) has been a commonly used, highly effective, and convenient induction regimen for both groups. Five-year overall survival (OS) rates for high-risk and standard-risk patients with RVD induction, followed by risk-adapted maintenance therapy, are 57 percent and 81 percent, respectively, and the 10-year OS rates are 29 percent and 58 percent, respectively.[1]

Many patients will relapse after initial treatment. The selection of first-line treatment for RRMM is influenced by whether the relapse is early or late and various other factors (Exhibit 1). Early relapse is one which occurs within 12 months of finishing initial treatment. The most important factor in choosing therapy is that the selected therapy has been shown to produce stable disease or better and is well tolerated.

The treatment options at relapse are enrollment in a clinical trial, stem cell transplant, and various regimens of proteasome inhibitors, dexamethasone (which has therapeutic effect on MM cells), immunomodulators, and targeted monoclonal antibodies. Bortezomib (Velcade®), carfilzomib (Kyprolis®), and ixazomib (Ninlaro®) are proteasome inhibitors which induce apoptosis of MM cells. Lenalidomide (Revlimid®) and pomalidomide (Pomalyst®) are immunomodulators which induce immune responses, prevent inflammation, and enhance the activity of T cells and natural killer (NK) cells. Daratumumab (Darzalex®) and isatuximab (Sarclisa®) are anti-CD38 monoclonal antibodies; CD38 is overexpressed on MM cells.

Exhibit 1: Factors to Consider for Treatment Selection

Disease-Related Factors	Treatment-Related Factors	Patient-Related Factors
• Nature of relapse	• Previous therapy	• Renal insufficiency
• Risk stratification	• Regimen-related toxicity	• Hepatic impairment
• Disease burden	• Depth and duration of previous response	• Comorbidities and frailty
• Disease staging	• Tumor burden at relapse	• Patient preferences

Elotuzumab (Empliciti®), a humanized IgG1 monoclonal antibody, directly activates NK cells through both the signaling lymphocytic activation molecule family member 7 (SLAMF7) pathway and Fc receptors. Elotuzumab also targets SLAMF7 on myeloma cells and facilitates the interaction with NK cells to mediate the killing of myeloma cells through antibody-dependent cellular cytotoxicity (ADCC).

If autologous stem cell transplant (ASCT) was not used as initial treatment, it can be utilized at first relapse. However, it may not be feasible, even if stem cells were stored, due to the patient's poor clinical condition or refractory disease. Progression –free survival (PFS) is usually shorter, but OS may be the same as with ASCT as part of initial therapy. Median PFS is approximately 16 months.[2,3] An ASCT can be done at the time of relapse even if used as initial therapy. The Emory University Winship Cancer Institute limits use of second ASCT for patients who have PFS on maintenance therapy of greater than 30 months.

The treatment options for early relapse used at Emory University Winship Cancer Institute are shown in Exhibit 2. Recent studies favor the use of daratumumab as part of the regimen based on response.[4,5] The National Comprehensive Cancer Network (NCCN) guidelines list several daratumumab regimens as Category 1 preferred regimens but does not specify any recommended regimen in early or late relapse.[6] Patients with RRMM will typically undergo multiple lines of therapy because the disease becomes resistant to various therapies and reemerges. Several therapies, including selinexor and belantamab mafodotin, have been FDA-approved for treating RRMM in heavily pretreated patients.

Selinexor (Xpovio®) reversibly inhibits nuclear export of tumor suppressor proteins (TSPs), growth regulators, and mRNAs of oncogenic proteins by blocking exportin 1 (XPO1). XPO1 inhibition by selinexor leads to accumulation of TSPs in the nucleus and reductions in several oncoproteins, such as c-myc and cyclin D1, cell cycle arrest, and apoptosis of cancer cells. It is FDA-approved in combination with dexamethasone for the treatment of adult patients with RRMM who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. In patients with penta-refractory disease, treatment with the combination of selinexor and dexamethasone resulted in a 26.2 percent overall response rate and a 4.4-month median duration of response.[7]

Belantamab mafodotin (Blenrep®) was FDA-approved in August 2020 for the treatment of adult patients with RRMM who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. It was conditionally approved based on response rate in Phase I and II trials; continued approval for this indication is contingent upon verification and description of clinical benefit in confirmatory trial(s). It is a B-cell maturation antigen (BCMA)-directed antibody and microtubule inhibitor conjugate. In an open-label, two-arm, Phase II study in 196 patients with disease progression after three or more lines of therapy and who were refractory to immunomodulatory drugs and proteasome inhibitors, and refractory or intolerant (or both) to an anti-CD38 monoclonal antibody with an Eastern Cooperative Oncology Group performance status of 0 – 2, 31 percent of 97 patients in the 2.5 mg/kg cohort and 34 percent of 99 patients in the 3.4 mg/kg cohort achieved an overall response.[8] Uniquely, this agent appears to cause ocular toxicity (keratopathy in 27%) in addition to the typical hematologic toxicities of MM treatment.

Numerous other agents are under development for treating RRMM. Venetoclax (Venclexta®) is

Exhibit 2: Emory Approach to Early Relapse

Clinical Trial Check if patient is t(11;14)			
Slow Indolent Relapse		**Aggressive Relapse**	
On Len maintenance	**No Len maintenance**	**On Len maintenance**	**No Len maintenance**
Dara/Pom/Dex	Dara/Len/Dex	Dara/Pom/Dex	Dara/Len/Dex
Ixazomib/Dex/higher dose Len*	Elo/Len/Dex	Car/Pom/Dex	Dara/Vel/Dex
Elo/Dex/higher dose Len	Car/Len/Dex		Car/Pom/Dex

Len = lenalidomide; Dara = daratumumab; Pom = pomalidomide; Dex = dexamethasone; Elo = elotuzumab; Car = carfilzomib; Vel = bortezomib

a selective and orally bioavailable small-molecule inhibitor of B-cell lymphoma two (BCL-2) currently FDA-approved for treating chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and acute myeloid leukemia (AML). It also can target BCL-2 in MM and is in trials. It has encouraging clinical efficacy in t (11;14) translocated MM as monotherapy and in a broader patient population in combination with bortezomib/dexamethasone.[9,10] Approximately 20 percent of myeloma patients will exhibit t (11;14) associated with high BCL-2 expression.

Iberdomide is an investigational immunomodulator that is a potent cereblon E3 ligase modulator.[11] This is the same mechanism of action as lenalidomide and pomalidomide, but this agent is more potent. It is in very early clinical trials and none have been published yet.

Cell-based immunotherapies, such as chimeric antigen receptor (CAR) T cells, are showing impressive activity in the RRMM setting. Challenges to their widespread use remain, including toxicity, manufacturing time, and cost. In a study of idecabtagene vicleucel (formerly bb2121), which targets BCMA, in 33 patients who had received a median of seven prior therapies, the objective response rate was 85 percent, including 45 percent with complete responses.[12] Six of the 15 patients who had a complete response have had a relapse since treatment. The median PFS was 11.8 months. All 16 patients who had a response (partial response or better) and who could be evaluated for minimal residual disease (MRD) had MRD-negative status ($\leq 10^4$ nucleated cells). CAR T-cell expansion was associated with responses, and CAR T cells persisted up to one year after the infusion.

In another Phase II trial in 128 R/R MM patients who had disease after at least three previous regimens including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody, idecabtagene vicleucel treatment resulted in a 73 percent overall response rate; 33 percent had a complete response or better.[13] MRD-negative status ($< 10^5$ nucleated cells) was confirmed in 26 percent who were treated and 79 percent of those with a complete response or better. The median PFS was 8.8 months. Common toxic effects included neutropenia (91%), anemia (70%), and thrombocytopenia (63%). Cytokine release syndrome was reported in 84 percent, including 5 percent who had events of Grade 3 or higher. Neurotoxic effects developed in 18 percent and were of Grade 3 in 3 percent; no neurotoxic effects higher than Grade 3 occurred. Cellular kinetic analysis confirmed CAR T cells in 59 percent at six months and 36 percent at 12 months after infusion. Other CAR T-cell therapies are also under investigation.

Conclusion

For early relapse of MM after initial management, daratumumab should be considered as the backbone of therapy, and which therapy to add to daratumumab will depend on prior therapy and resistance. Management of refractory MM remains a challenge and needs new agents to counter resistance. Cell therapy is on the way, but further research needs to be done to improve outcomes and reduce toxicity.

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Recent Advances in the Treatment and Management of NASH

M. Romina Lomonaco, MD

For a CME/CEU version of this article, please go to
http://www.namcp.org/home/education, and then click the activity title.

Summary

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the United States (U.S.) and is soon to be the leading cause of liver transplantation. Patients at the greatest risk are those with obesity and type 2 diabetes. Weight loss and several pharmacological treatments can often be successful to reverse steatohepatitis and prevent disease progression.

Key Points

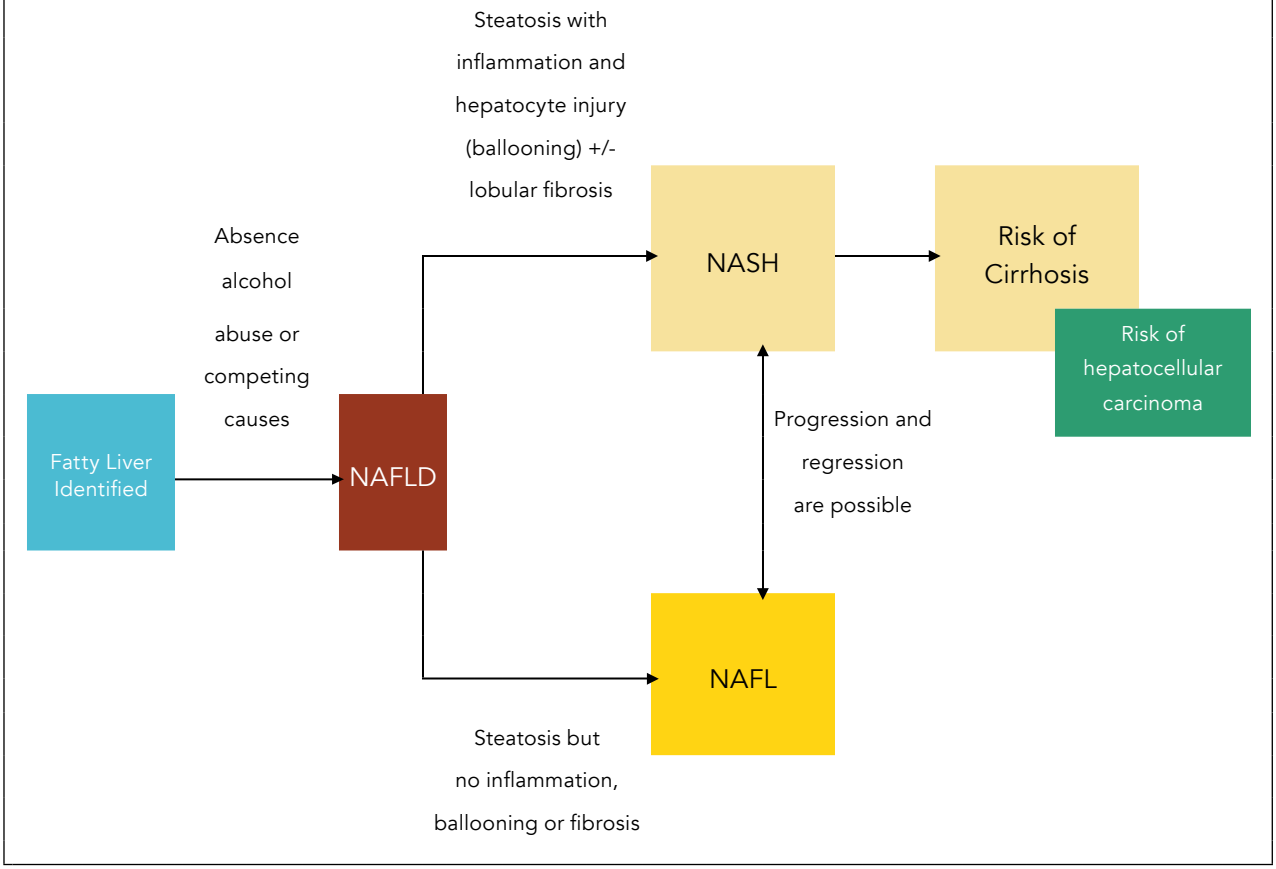
- Nonalcoholic fatty liver disease is an underappreciated liver disease and a common complication of type 2 diabetes and obesity.
- Primary treatments are weight loss and certain diabetes medications.
- It is important to screen for this disease in everyone with type 2 diabetes or those with elevated liver function tests or incidental finding of fatty liver.

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) is a chronic liver condition characterized by hepatic fat accumulation (in the absence of ethanol abuse or other identifiable causes) and insulin resistance. It is frequently associated with impaired glucose tolerance or type 2 diabetes (T2D), is the most common chronic liver disease in the U.S., and is soon to be the leading cause of liver transplantation.[1] Steatosis may range from simple steatosis to nonalcoholic steatohepatitis (NASH) with progressive liver damage with necrosis, inflammation and frequently fibrosis. NASH is a risk factor for cirrhosis and liver cancer. Exhibit 1 shows the progression from NAFLD to NASH.[1] Insulin resistance and adipose tissue dysfunction appear central to the pathogenesis of NASH.

The two major risk factors for NAFLD are obesity and T2D. The prevalence of NASH in the U.S. among those with T2D is 51.8 percent, which is similar to the global prevalence of 55 percent.[2] Over 18 million people in the U.S. are living with T2D and NAFLD, of which 6.4 million have NASH. Twenty-year costs for NAFLD in these patients have been estimated at $55.8 billion.[3] During the next 20 years, NASH with T2D will account for 65,000 transplants, 812,000 liver-related deaths, and 1.37 million cardiovascular-related deaths.

The American Diabetes Association guidelines recommend that all patients with diabetes or pre-diabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound be evaluated for NASH and liver fibrosis.[4] It is important to note that as high as 50 percent of those with T2D and obesity can have NAFLD despite normal liver enzymes.[5] A diagnosis algorithm is presented in Exhibit 2.[6] Fibrosis can be diagnosed with biomarkers, ultrasound, or other noninvasive imaging based analyses, but referral to a liver specialist and a liver biopsy may be required for definitive diagnosis. Vibration-controlled transient elastography (FibroScan®) is the most widely used noninvasive test by hepatologists. Training is easy, it is simple to use, there is a large amount of supporting literature, the test is not time-consuming and is available at point of care. Disadvantages are that the device is expensive (although testing affordable) and less accurate in cases of mild fibrosis than other noninvasive tests. Liver biopsy remains the suboptimal gold standard to characterize liver histology in NAFLD and NASH. It confirms the diagnosis and staging of disease and determines prognosis by severity of liver injury and fibrosis. Advanced fibrosis (stage F3 – F4) on liver biopsy

Exhibit 1: Fatty Liver, NAFLD, NAFL, and NASH[1]



NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis

independently predicts all-cause and liver-related mortality in NASH.[7] Limitations of biopsy are the high cost, potential complications, and sampling or reader error.

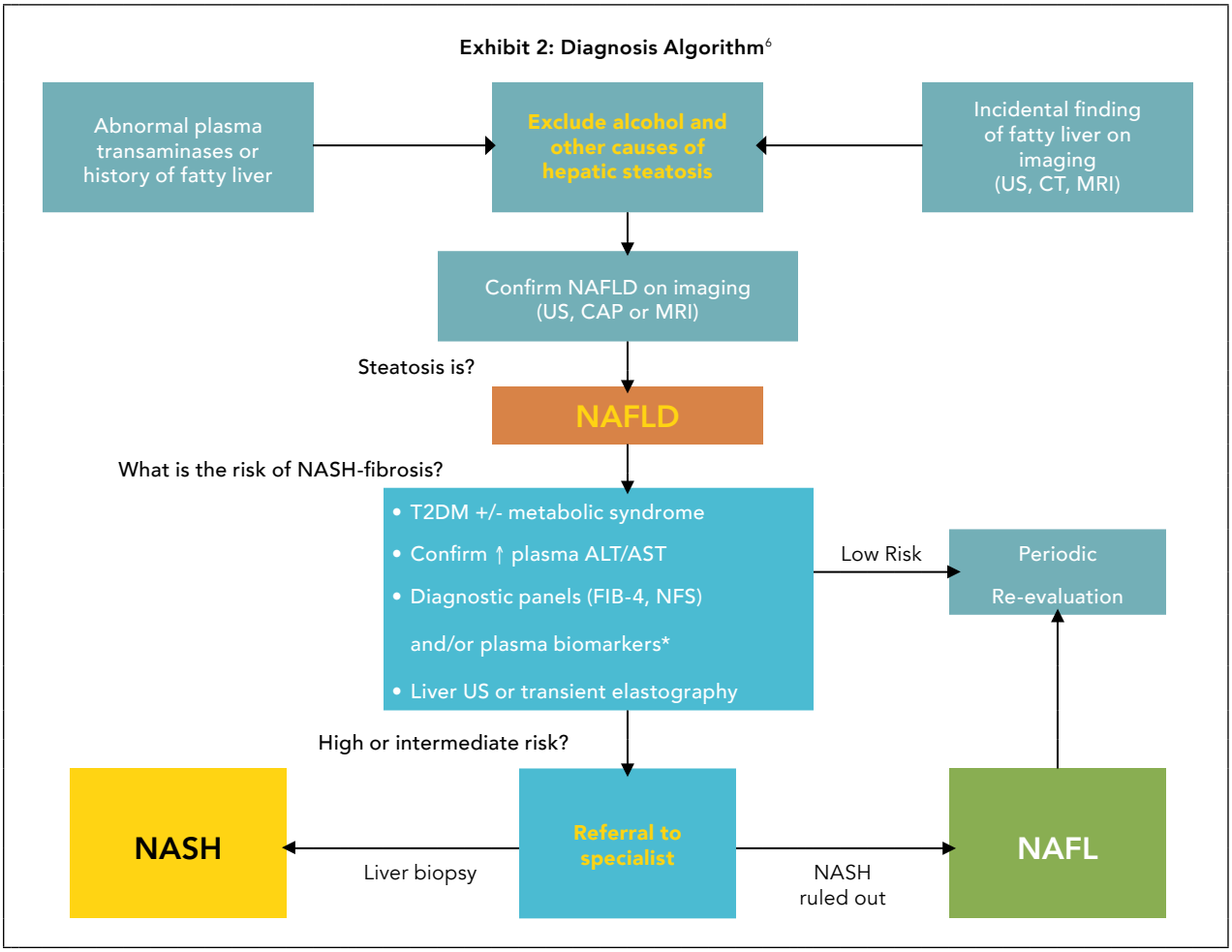
The American Association for the Study of Liver Diseases publishes guidelines on the diagnosis and management of NAFLD.[8] The management of NAFLD should consist of treating liver disease as well as the associated metabolic comorbidities such as obesity, hyperlipidemia, insulin resistance, and T2D. Given that patients with NAFLD without NASH or any fibrosis have excellent prognosis from a liver standpoint, pharmacological treatments aimed primarily at improving liver disease should generally be limited to those with biopsy-proven NASH and fibrosis.[8]

The primary treatment of NAFLD and/or NASH is lifestyle management composed of diet, exercise, and weight loss. Three to 5 percent loss of starting body weight is needed to improve steatosis, but 7 percent to 10 percent is the minimal amount to improve the majority of the histopathological features of NASH, including fibrosis.[8] Exercise alone may prevent or reduce steatosis, but its ability to improve other aspects of liver histology remains unknown. The probability of reaching NASH resolution, fibrosis regression, and steatosis improvement in patients with NASH under lifestyle intervention according to percentage of weight loss is shown in Exhibit 3.[9]

Bariatric surgery can be considered in otherwise eligible obese individuals with NAFLD or NASH.[8] The guidelines note that it is premature to consider bariatric surgery as an established option to treat NASH. The type, safety, and efficacy of bariatric surgery are not established in obese individuals with cirrhosis from NAFLD. In patients with compensated NASH or cryptogenic cirrhosis, bariatric surgery may be considered on a case-by-case basis.

Several pharmaceuticals have been considered for treating NASH. Pioglitazone improves liver histology, including advanced fibrosis, in patients with and without T2D with biopsy-proven NASH.[7] In one trial, among patients randomly assigned to pioglitazone,

Exhibit 2: Diagnosis Algorithm[6]



NAFLD = non-alcoholic fatty liver disease; NAFL = non-alcoholic fatty liver; NASH = non-alcoholic steatohepatitis; US = liver ultrasound; CAP = controlled attenuation parameter; MRI = magnetic resonance imaging (used largely in research settings); NFS = NAFLD fibrosis score
*Plasma biomarkers (several commercial ones available and others are in development).

58 percent achieved the primary outcome, and 51 percent had resolution of NASH ($p < 0.001$ for each versus placebo, Exhibit 4).[10] Pioglitazone treatment also was associated with improvement in individual histologic scores, including the fibrosis score (treatment difference, - 0.5; $p = 0.039$); reduced hepatic triglyceride content from 19 percent to 7 percent ($p < 0.001$); and improved adipose tissue, hepatic, and muscle insulin sensitivity ($p < 0.001$ versus placebo for all). Risks and benefits of this agent should be discussed with each patient. Pioglitazone is not FDA-approved for treatment of NAFLD or NASH. Common adverse events with pioglitazone include weight gain and lower limb edema. Long-term, pioglitazone is associated with osteoporosis so bone density should be monitored.

Glucagon-like peptide one receptor antagonists (GLP-1RAs) are another possible option because of their effect on weight and liver histology.[11] In one trial in 52 patients, liraglutide compared to placebo was safe, well tolerated, and led to major histological improvements (Exhibit 5).[12] The guidelines state it is premature to consider GLP-1RAs to treat patients with NAFLD or NASH but many clinicians still use them for this purpose.

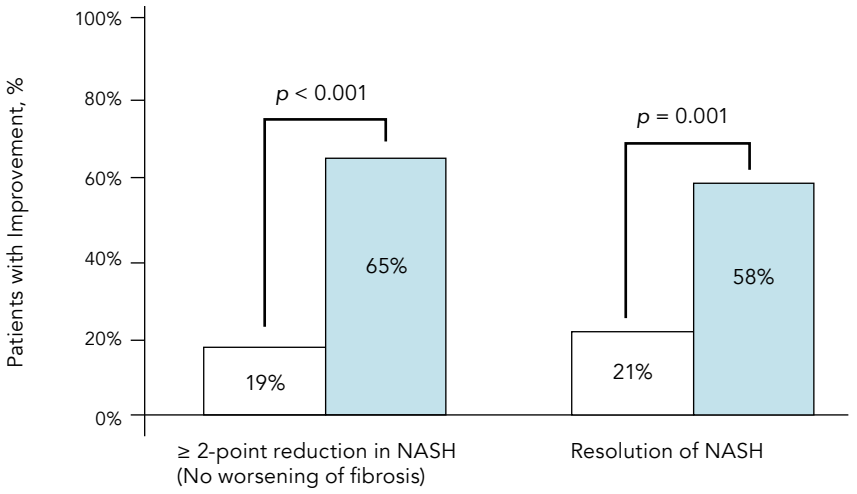
The sodium-glucose co-transporter two (SGLT2) inhibitors improve glycemia by increasing urinary glucose excretion, reduce body weight and blood pressure, and improve cardiovascular and renal outcomes in T2D. In several studies, SGLT2i reduced hepatic steatosis more than expected for the rather modest weight loss, suggesting additional weight-independent mechanisms.[13] Furthermore, a reduction of liver fat may not necessarily be proportional to the improvement in necroinflammation or fibrosis, as has been suggested with pioglitazone.[13] This class requires further investigation for treatment of NAFLD and NASH and are not included in the most recent guidelines.

Vitamin E, at 800 IU/day, improves liver histology

Exhibit 3: Probability of Improvement with Lifestyle Intervention for One year in Adults[9]

Percentage weight loss (WL)	5%	7%	10%
NASH-resolution	10%	26%	64%	90%
FIBROSIS-regression	45%	38%	50%	81%
STEATOSIS improvement	35%	65%	76%	100%
Percentage of patients achieving WL	70%	12%	9%	10%

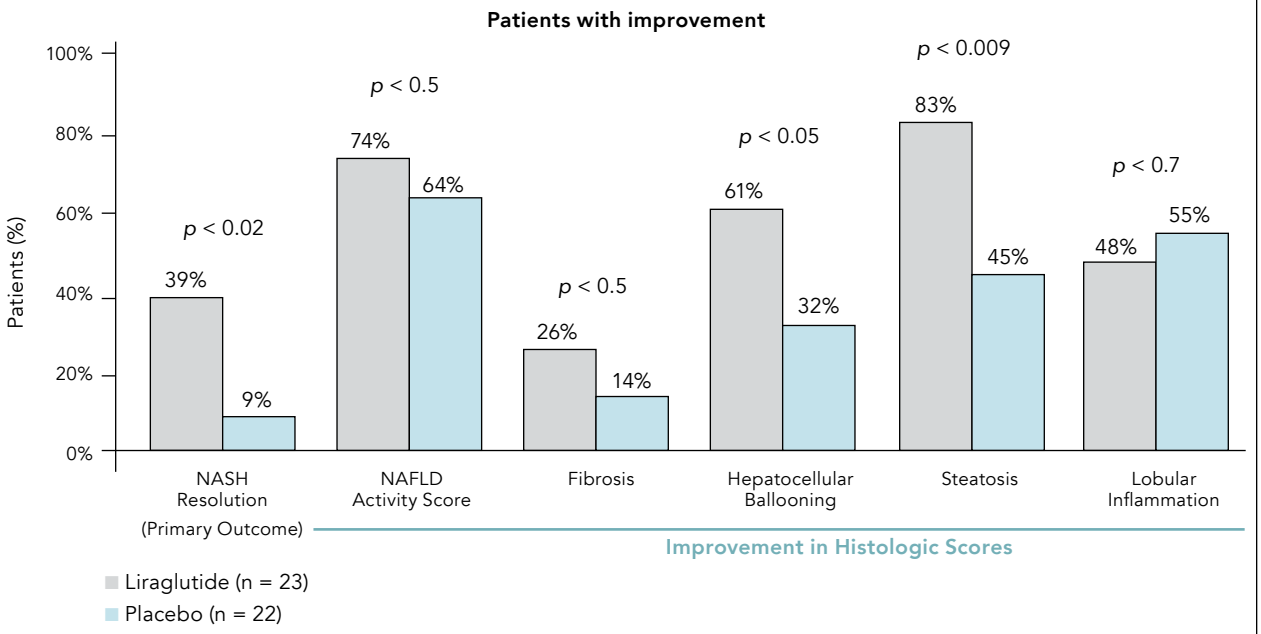
Exhibit 4: Long-term Effect of Pioglitazone in NASH versus Placebo[10]



in adults with NASH but without diabetes.[8] Until further data supporting its effectiveness become available, it is not recommended for NASH in patients with diabetes and is also not recommended without a liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis. In those with T2D a recent trial found that vitamin E 400 IU twice a day plus pioglitazone 45 mg/day reduced the NAFLD activity score without worsening of fibrosis better than placebo or vitamin E alone (54% versus 19% versus 31%, respectively).[14] The guidelines also address the use of metformin, although effective for T2D it is not recommended specifically for treating NASH in adult patients. No improvements in liver histology have been shown with metformin treatment.

In addition to current treatments for T2D, other agents are being investigated which target NAFLD and NASH. Farnesoid X receptor agonists, thyroid hormone receptor beta selective agonists, and fibroblast growth factor 21 agonists are all under study for treating fibrosis. For example, obeticholic acid is a farnesoid X receptor agonist which has been submitted to the FDA for approval. In June 2020, the FDA determined that the benefit of obeticholic acid based on surrogate histopathologic endpoints from a Phase III trial remained uncertain and did not outweigh potential risks sufficiently to support accelerated approval of the treatment for patients with fibrosis due to NASH.[15,16] The FDA recommended the company submit additional analysis on efficacy and safety data on the trial to support accelerated approval. Additionally, the FDA said the long-term outcomes phase of the study should be continued.

Exhibit 5: Changes in Liver Histologic Features at Week 48 with Liraglutide[12]



Conclusion

Everyone caring for patients with diabetes needs to embrace the evolving clinical challenge posed by NAFLD and NASH, needs to educate their patients, and needs to be proactive in the diagnosis and monitoring of patients with this underappreciated complication of T2D and obesity. Current treatments include lifestyle changes to induce weight loss, pioglitazone, vitamin E, and GLP-1RA. More novel therapies are on the horizon.

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Exploring New Treatment Paradigms in Prostate Cancer: Current and Emerging Treatment Strategies to Improve Patient Care

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For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

Treatment strategies for prostate cancer have evolved rapidly and continue to expand. Improving survival with metastatic prostate cancer is a major focus. Agents now approved for both non-metastatic and metastatic castration-resistant prostate cancer will result in survival advances.

Key Points

- Apalutamide, enzalutamide, and darolutamide improve metastatic-free survival in non-metastatic castration-resistant prostate cancer.
- Olaparib and rucaparib are options for patients with metastatic castration-resistant prostate cancer with somatic or tumor DNA repair defects.

THE AMERICAN CANCER SOCIETY'S estimates for prostate cancer in the United States (U.S.) for 2021 are 248,530 new cases of prostate cancer and 34,130 deaths.[1] The five-year survival rate for this cancer has increased significantly over the years from 68 percent to 98 percent.[2] Although many men will have their prostate cancer found early and successfully treated, survival with newly diagnosed metastatic prostate cancer remains disappointing. One trial found that the median failure-free survival (FFS) was 11 months; two-year FFS was 29 percent. Median overall survival (OS) was 42 months; two-year OS was 72 percent.[3] Survival time was influenced by performance status, age, Gleason score, and metastases distribution.

The most common sites for prostate cancer metastases are bone and lymph nodes. The majority of men with metastatic disease have bone-only or bone dominant disease. Those with soft tissue disease have better survival than those with bone only disease; those with bone and soft tissue disease have the worst survival rate.[3]

Androgen deprivation therapy (ADT) is a mainstay of treatment for metastatic disease. ADT refers to medical castration (with a gonadotropin-releasing hormone agonist or antagonist) or bilateral orchiectomies. It results in responses in most men, but all men eventually progress to castration-resistant prostate cancer (CRPC). CRPC is defined by disease progression despite ADT with castrate level testosterone levels and may present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases.[4]

Metastatic CRPC (mCRPC) can be treated with various therapies. Six agents are approved in mCRPC based on improved OS. This includes chemotherapy (docetaxel, cabazitaxel), androgen receptor targeting agents (abiraterone acetate, enzalutamide), sipuleucel-T, and Radium-223. There is limited information about optimal sequencing of treatment in mCRPC. Choice of initial systemic treatment for CRPC depends on many factors, including prior systemic treatments, site and extent of disease

Exhibit 1: Comparing Trials in nmCRPC[7-11]

SPARTAN Apalutamide	• 72% reduction of distant progression or death • Median MFS: APA 40.5 versus PBO 16.2 months • 24-month MFS benefit • 25% reduction in risk of death
PROSPER Enzalutamide	• 71% reduction of distant progression or death • Median MFS: ENZA 36.6 versus PBO 14.7 months • 22-month MFS benefit • 27% reduction in risk of death • Median OS: ENZA 67 months versus PBO 56.3
ARAMIS Darolutamide	• 59% reduction of distant progression or death • Median MFS: DARO 40.4 versus PBO 18.4 months • 22-month MFS benefit

nmCRPC = nonmetastatic castration-resistant prostate cancer; MFS = metastasis-free survival; PBO = placebo; OS = overall survival

involvement, comorbidities, and presence or absence of symptoms.

Those with CRPC can also have nonmetastatic CRPC (nmCRPC). This is defined as a rising PSA level despite ongoing ADT, castrate level testosterone levels, and no detectable metastases by conventional imaging (bone scan, CT, or MRI). Most patients with nmCRPC are presumed to have occult metastatic disease not detected by conventional imaging. This important patient population was not included in pivotal studies leading to approval of a variety of drugs for mCRPC. Men with nmCRPC are at significant risk for metastatic disease and prostate cancer-specific death.[5] Prevention of detectable metastases in the nmCRPC population represents an important unmet medical need.

In those with nmCRPC, the PSA doubling time is associated with time to metastasis or death. In one trial, a 6.3 month or less doubling time carried the most risk for developing metastasis or dying, and greater than 18.8 months was lowest risk.[6] Doubling time is used to decide whether to change therapy for nmCRPC.

Apalutamide (Erleada®), enzalutamide (Xtandi®) and darolutamide (Nubeqa®) are next- generation androgen receptor inhibitors that are FDA-approved for treating nmCRPC in combination with ADT. Darolutamide is structurally distinct from apalutamide and enzalutamide, is characterized by low blood-brain barrier penetration, and may have improved tolerability. In a Phase III trial involving men with nmCRPC and a PSA doubling time of 10 months or less, metastasis-free survival (MFS) was significantly longer with darolutamide than with placebo.[7] The median MFS was 40.4 months with darolutamide, as compared with 18.4 months with placebo ($p < 0.001$). Darolutamide was also associated with benefits with regard to all secondary endpoints, including overall survival, time to pain progression, time to cytotoxic chemotherapy, and time to a symptomatic skeletal event.

Exhibit 1 compares the trials in nmCRPC with apalutamide, enzalutamide, and darolutamide.[7-11] Overall, improvements in MFS were large and consistent across subgroups in each of the three pivotal studies. Clinical benefit was supported by improvements in key secondary endpoints, including late clinical events that followed detection of metastases in each of the three studies. Benefit to risk appears favorable for all three drugs. Treatment was associated with maintenance of health-related quality of life.

In a meta-analysis of the three trials compared in Exhibit 1, apalutamide and enzalutamide were more efficacious agents for nmCRPC, while darolutamide appeared to have the most favorable tolerability

profile.[12] For MFS, apalutamide, darolutamide, and enzalutamide were significantly more effective than placebo, and apalutamide emerged as the best option ($p = 0.8809$). For PSA progression-free survival, all three agents were statistically superior to placebo, and apalutamide emerged as the preferred option ($p = 1.000$). For adverse events (including all, Grade 3 or Grade 4, Grade 5, and discontinuation rates), darolutamide was the best option. Abiraterone therapy does require concurrent prednisone and causes fluid retention, hypertension, and hypokalemia. There is a risk of seizures and other CNS adverse events with enzalutamide.

The poly (ADP-ribose) polymerase (PARP) inhibitors are the newest class of medication to be approved for the treatment of metastatic prostate cancer. PARP is a versatile enzyme with several key physiological functions, among which is single-strand DNA break repair by the base excision repair pathway. The role of PARP proteins in DNA repair is of particular interest because certain tumors defective in homologous recombination repair (HRR) mechanisms, may rely on PARP-mediated DNA repair for survival, and are sensitive to its inhibition. The prevalence of tumor DNA repair defects in patients with mCRPC is 10 to 20 percent.[13,14] The most commonly altered DNA repair genes in prostate cancer are breast cancer two (BRCA2), BRCA1, and ataxia-telangiectasia mutated (ATM).[14]

Olaparib (Lynparza®) and rucaparib (Rubraca®) are the two PARP inhibitors which are FDA-approved for treating prostate cancer. Olaparib improves radiologic progression-free survival (rPFS) in patients with mCRPC, DNA repair deficiency, and disease progression after docetaxel and either abiraterone or enzalutamide (7.4 months versus 3.6 months control group).[15] There was significantly improved median overall survival (OS) with olaparib versus enzalutamide/abiraterone in those with BRCA2, BRCA1, and ATM mutations (19.1 months versus 14.7 months; $p = 0.0175$), despite crossover of 67 percent of patients from the control arm to olaparib.[16] In May 2020, the FDA approved olaparib for the treatment of patients with pathogenic germline or somatic HRR gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone.

Rucaparib was studied in 115 patients with mCRPC that previously progressed on an androgen receptor-directed therapy or one taxane-based chemotherapy for CRPC and harbored a BRCA gene alteration.[17] The primary endpoint of objective response rate (ORR) was met in 33 percent of patients and a secondary endpoint of 50 percent reduction in PSA was achieved by 55 percent of patients. In addition, 25 percent of patients had stable disease. Based on this data, rucaparib was approved by the FDA in May 2020 for mCRPC harboring a BRCA1 or BRCA 2 gene alteration with disease progression on taxane and androgen receptor-directed therapy. The approval was an accelerated approval based on objective response rate and duration of response. Continued approval for this indication is contingent upon data from the ongoing TRITON3 trial, a Phase III trial that also includes those with ATM mutation.

Preliminary evidence suggests that other PARP inhibitors (niraparib and talazoparib) are active in prostate cancer. Ongoing studies will evaluate PARPi in other settings and in combination with other drugs.

Conclusion

The treatment of metastatic prostate cancer continues to evolve. There are now therapies available for nmCRPC and HRR mutated mCRPC. Hopefully, these newer treatments will help improve survival rates.

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New Approaches in the Treatment and Management of Idiopathic Pulmonary Fibrosis

Steven D. Nathan, MD

For a CME/CEU version of this article, please go to
http://www.namcp.org/home/education, and then click the activity title.

Summary

Idiopathic pulmonary fibrosis (IPF) is a progressive, fatal disease. At this time, there are two antifibrosis therapies which slow the progression of the disease. A new therapy was recently approved for treating pulmonary hypertension secondary to IPF. Numerous therapies are on the horizon to better target the underlying pathologic process.

Key Points

- Early accurate diagnosis is critical and early treatment is very important.
- The key to successful treatment is maintaining patients on therapy.
- Antifibrotic therapy improves survival.
- Inhaled treprostinil represents a new pathway to target.
- Combination therapy is in the future.

IDIOPATHIC PULMONARY FIBROSIS (IPF) is a distinct type of chronic fibrosing interstitial pneumonia of unknown cause that is limited to the lungs. IPF occurs primarily in older adults and is more common in men. There is a history of smoking in two-thirds of patients. This is a uniformly fatal disease, which also causes significant morbidity. Median survival after diagnosis is 2.5 to 5 years. The only cure for the disease is lung transplantation.

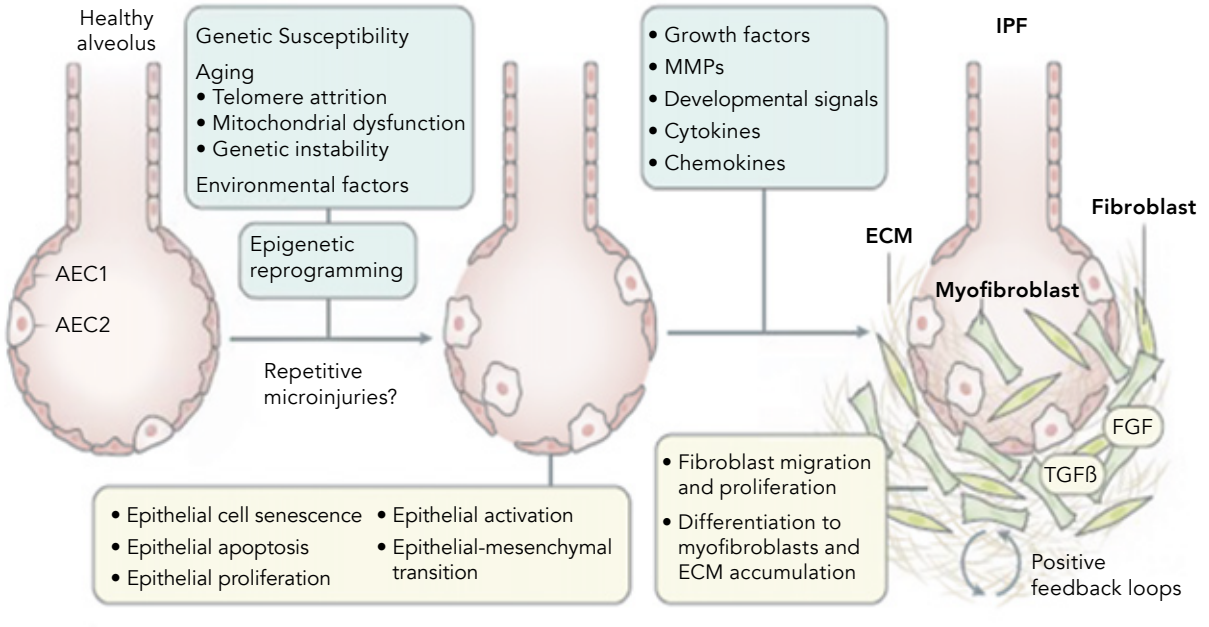
The diagnosis of IPF can be difficult, but an accurate diagnosis is very important.[1] Multidisciplinary diagnosis, which uses pulmonology, radiology, pathologist, and rheumatology specialists, improves diagnostic accuracy. IPF is diagnosed by ruling out other causes of interstitial lung disease and the presence of typical findings on high resolution CT and histopathologic pattern of usual interstitial pneumonia (UIP).[2] Sometimes a lung biopsy is required when the pattern in the lung is probable UIP or indeterminate.

The etiology of IPF remains incompletely understood; previously it was thought to be an inflammatory condition leading to fibrosis. The current understanding is that the cause is a repetitive injury with an abnormal healing response in genetically susceptible individuals.[1] It is thought that the injury to the epithelial cells in the lung leads to a cascade of growth factors and coagulants, resulting in an invasion of myofibroblasts and ultimately fibrosis instead of normal repair (Exhibit 1).[3] Healthy tissue is replaced by altered extracellular matrix and alveolar architecture is destroyed, which leads to decreased lung compliance, disrupted gas exchange, and ultimately respiratory failure and death.

The course of IPF varies among patients. Some will have rapid progression, while others have a slower disease course. Acute exacerbations can also cause step like drops in lung function and are a risk factor for dying. Median survival in the pre-antifibrotic therapy era was 48 months.[4]

Because there are now effective treatments and treatments which are known to cause harm, early and accurate diagnosis is more important than ever. The combination of azathioprine, prednisone, and

Exhibit 1: Pathology of IPF[3]



AEC = alveolar epithelial cell; MMPs = matrix metalloproteinases; ECM = extracellular matrix; FGF = fibroblast growth factor; TGFß = Transforming growth factor-ß

N-acetylcysteine was commonly used for IPF before antifibrotics became available. This combination should no longer be used because it has been shown to increase risk of hospitalization and death.[5]

The goal with therapy in the early stages of the disease is to slow loss of lung function. Two disease-modifying antifibrotics, pirfenidone (Esbriet®) and nintedanib (Ofev®), have been shown to significantly reduce lung function decline, reduce mortality, increase progression-free survival, and improve six-minute walk test results.[6,7] The 2015 IPF treatment guidelines conditionally recommend the use of these two agents and GERD treatment.[8] These guidelines also recommended against use of macetetain, bosentan, and sildenafil ,which are approved for pulmonary hypertension and are not effective in IPF. In the end-stage of the disease, patients can develop pulmonary hypertension and then the specific agents for pulmonary hypertension may be effective.

Antifibrotic therapy should be started as soon as the diagnosis is confirmed and continued indefinitely as long as the selected agent is tolerated. Mortality benefits have been shown with therapy that has been continued even when lung function continues to decline.[9] Two registry trials have also shown survival benefits with antifibrotic therapy.[10,11] In the Czech registry study, pirfenidone significantly increased five-year overall survival over no-antifibrotic treatment (55.9% versus 31.5% alive, $p = 0.002$).[11]

The next iteration of IPF management will likely be combination therapy. Pirfenidone and nintedanib in combination have been shown to be safe and effective based on one trial.[12] Mean changes from baseline in forced vital capacity (FVC) at week 12 were -13.3 (±17.4) ml and -40.9 (±31.4) ml in patients treated with nintedanib and pirfenidone (n = 48) and nintedanib alone (n = 44), respectively. On-treatment gastrointestinal adverse events were reported in 69.8 percent of patients treated with the combination and 52.9 percent treated with nintedanib alone. Longer term larger studies are needed to see if survival is improved with combination antifibrotic therapy.

There are also trials combining pirfenidone or nintedanib with sildenafil, which is used for pulmonary hypertension. In patients with IPF and diffusion capacity of the lungs for carbon monoxide (DlCO) of 35 percent or less of the predicted value, nintedanib plus sildenafil 20 mg three times daily did not provide a significant benefit in respiratory symptom scores as compared with nintedanib alone (-1.28 points and -0.77 points, respectively; $p = 0.72$).[13] In a subgroup analysis of this trial, nintedanib plus sildenafil reduced FVC decline numerically but not statistically in those who also had evidence of right heart dysfunction.[14] Changes in brain natriuretic peptide (BNP) were significant in those with concomitant right heart dysfunction (-119.9 ng/L versus -3.6 ng/L, $p < 0.01$).

Both pirfenidone and nintedanib are both being studied in other interstitial lung diseases (ILD). This includes systemic sclerosis-related, rheumatoid arthritis-related, unclassifiable progressive fibrosing, and other ILD. In several studies, the effect of nintedanib appears consistent over a variety of fibrotic lung disorders.[15,16] Antifibrotic therapies may be used off-label for these other ILD.

Inhaled treprostinil (Tyvaso®) is the newest therapy approved for IPF. It was FDA-approved in April 2021 for pulmonary hypertension associated with ILD. Treprostinil is a prostacyclin analogue which causes direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. It has been available for use in treating pulmonary arterial hypertension since 2002. In the trial that led to the new FDA approval, inhaled treprostinil significantly improved six-minute walk distance versus placebo (by 31 meters), and showed benefit across several subgroups, including etiology of pulmonary hypertension-associated ILD, disease severity, age, gender, baseline hemodynamics and dose.[17] There was a reduction of 15 percent in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels from baseline with inhaled treprostinil, as compared with an increase of 46 percent with placebo ($p < 0.001$). Clinical worsening occurred in 22.7 percent in the treprostinil group, as compared with 33.1 percent in the placebo group ($p = 0.04$). There were also improvements in secondary endpoints including time to first clinical worsening event, change in peak six-minute walk distance at 12 weeks, change in the six-minute walk distance at 15 weeks, placebo-corrected improvements in FVC and fewer exacerbations of underlying lung disease. The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea.

Clinicaltrials.gov lists over 200 ongoing studies in IPF. New molecules in development target not only the deposition of extracellular matrix, but also upstream pathways including those mediated by the immune system and many are biologics. For example, pamrevlumab, an anti-connective tissue growth factor therapy, reduced the decline in the percentage of predicted FVC by 60.3 percent at week 48 compared to placebo in a Phase II trial.[18] The proportion of patients with disease progression was lower in the pamrevlumab group than in the placebo group at week 48 (10.0% versus 31.4%; $p = 0{\cdot}013$). This agent is currently in Phase III trials.

Conclusion

IPF is a complex, heterogenous disease. Early accurate diagnosis is critical, and early treatment is very important. The key to successful treatment is maintaining patients on antifibrotic therapy which has been shown to improve survival. Inhaled treprostinil represents a new pathway to target. Combination therapy is in the future, and exciting new agents are being developed.

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Effective Ways to Manage Insomnia: Improving Outcomes through Optimal Treatment Strategies

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For a CME/CEU version of this article, please go to
http://www.namcp.org/home/education, and then click the activity title.

Summary

Insomnia is not just an issue with sleeping; it is a chronic disorder that significantly impacts patient health and well-being and has societal impact. Management of insomnia can be accomplished with cognitive behavior therapy and medications.

Key Points

- Insomnia has significant consequences for individuals and society.
- Evidence-based treatments include Cognitive Behavioral Therapy for Insomnia (CBT-I) and FDA-approved medications.
- Treatment choices should be personalized for individual patients.
- New medications target key sleep-wake regulation processes to optimize efficacy and safety.

INSOMNIA IS A COMMON SLEEP DISorder defined as difficulty falling asleep, difficulty staying asleep, or early awakenings with inability to return to sleep occurring for at least three months (Exhibit 1).[1,2] Approximately 30 percent of the general population in the United States (U.S.) has insomnia symptoms.[3] Six to 10 percent of the population has associated symptoms of daytime functional impairment (insomnia disorder).[3] The prevalence of insomnia is up to 50 percent in clinical practices where patients have comorbid medical and mental health conditions.

A study attempted to track the natural history of insomnia by estimating the incidence per annum of acute insomnia and to what extent those that develop acute insomnia recover good sleep or develop chronic insomnia. As shown in Exhibit 2, this study found that over one year 1.7 percent of subjects initially labeled as good sleepers developed incident chronic insomnia and 27 percent developed acute insomnia.[4] Of those with acute insomnia, almost 7 percent developed chronic insomnia. The risk factors for developing chronic insomnia are shown in Exhibit 3.

Insomnia does not just cause sleep issues. There are numerous complications including interpersonal, social, and occupational problems. There is increased risk for major depression, anxiety, hypertension, myocardial infarction, cardiometabolic syndrome, medication misuse, alcohol use, caffeine and stimulant use, and reduced quality of life.[5-7] Insomnia leads to significant societal burden and costs.[8,9] Direct costs include treatment costs and health care utilization for outpatient visits, emergency room visits, and hospitalizations.[10,11] Indirect costs include absenteeism, presenteeism (decreased productivity), lost income, vehicular crashes, and home and workplace accidents.

Untreated insomnia increases all-cause health care utilization/costs among Medicare beneficiaries utilization across all point of service locations (inpatient, emergency department, outpatient, and prescriptions).[12] In an adult managed care population, untreated insomnia was associated with 26 percent higher costs compared to those without insomnia.[13] Twelve months after diagnosis, insomnia was associated with 46 percent higher costs compared to those without insomnia. Health in the period following the insomnia diagnosis appears to decline relatively more than in members without an insomnia diagnosis.

Insomnia pathophysiology is multifactorial.

Exhibit 1: Insomnia Disorder Diagnostic Criteria[1,2]

Insomnia Complaint
• Difficulty initiating sleep
• Difficulty maintaining sleep
• Early-morning awakening
Daytime Consequences or Impairment
• Fatigue or malaise
• Attention, concentration or memory
• Performance (social, family, occupational, academic)
• Mood disturbance and irritability
• Daytime sleepiness
• Behavioral disturbances (hyperactivity, impulsivity, aggression)
• Motivation, energy or initiative
• Concerns or dissatisfaction with sleep
PLUS
• Adequate opportunity and circumstances for sleep
• Occurs at least three nights per week
• For at least three months
• Not better explained by another sleep-wake disorder, effects of a substance or medication, or coexisting mental disorders or medical conditions.

Overarching theoretical models are that insomnia results from hyperarousal. Cognitive processes and psychological conditioning lead to heightened anxiety, excessive worry, preoccupation with sleep difficulty, and perceived consequences occur. Sleep difficulty is conditioned by bedtime routines and failed attempts to sleep. Physiological processes also contribute by elevated arousal during both day and night in those with chronic insomnia; thus, it is a 24-hour disorder.[14] Those with chronic insomnia have an elevated sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis during sleep and waking. There is an increased heart rate; altered heart rate variability; increased whole-body metabolic rate; elevated cortisol, adrenocorticotropic hormone, and corticotropin releasing factor levels; increased body temperature; increased high-frequency electroencephalogram activity; and heightened metabolic activity during sleep and waking on brain scans.

There are several published clinical management guidelines for chronic insomnia, including ones from the American Academy of Sleep Medicine and American College of Physicians.[15-17] All of the guidelines recommend multifactorial treatment which includes promoting healthy sleep habits (sleep hygiene), education about sleep, optimizing treatment of comorbid conditions which contribute to sleep issues, behavioral strategies, and pharmacotherapy if necessary.

Healthy sleep habits are an essential component of all chronic insomnia treatment approaches. Recommendations should include schedule regularity, bedtime routines, bedroom environment (light, noise, temperature), daytime activities, exercise, light exposure, and potential effects of substances (alcohol, caffeine).

Cognitive Behavioral Therapy for Insomnia (CBT-I) is an evidence-based intervention as first-line therapy for all patients. It is a multimodal intervention of sleep hygiene education, cognitive strategies, sleep restriction, stimulus control, relaxation, and paradoxical intention. Traditional CBT-I involves six to eight individual or group sessions with a certified therapist, typically in person, and produces durable improvements in sleep onset and maintenance; however, there is limited availability of providers in many areas.[18]

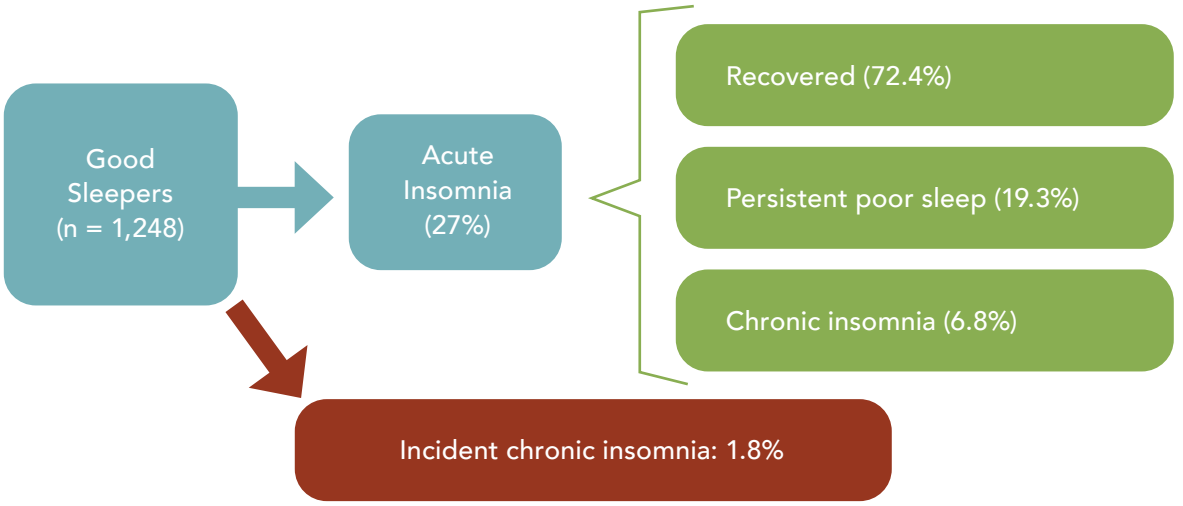
An alternative to CBT-I is Brief Behavioral Treatment of Insomnia (BBTI), which is also evidence-based. This is a four-session treatment approach where two sessions are delivered face-to-face and two by telephone by a non-psychologist health professional. It can be delivered in general medical settings and includes behavioral guidelines targeting homeostatic and circadian drives. BBTI results in improvement in sleep onset and maintenance.[19]

Available alternative delivery strategies for behavioral interventions include online self-directed, telemedicine, or telephone CBT-I programs; CBT-I phone applications; and self-help CBT-I books. Online delivery of a comprehensive CBT-I program has been shown to be as effective as in-person delivery and is an option for expanding access to this type of care, especially to areas lacking qualified therapists.[20]

Pharmacotherapy for insomnia includes unregulated complementary and alternative medicines, over-the counter-medications, off-label prescription medications with sedating effects, and FDA-approved agents.

Complementary and alternative medicines include melatonin and various herbals, including valerian. There are a huge number of these products marketed as sleep aids. There is limited efficacy data and some

Exhibit 2: The Natural History of Insomnia[4]



safety concerns with all these agents. None are regulated by the FDA, so there can be safety questions related to purity, concentration, and toxicity.[21] Over-the-counter sleep aids primarily contain sedating antihistamines, such as diphenhydramine, which are histamine H1 receptor antagonists and muscarinic acetylcholine receptor antagonists. These products are regulated by the FDA; therefore, composition, dosing, manufacturing, labeling, and marketing are controlled. These are available as an antihistamine alone or combined with analgesics. Major issues with these products are long half-life, especially in the elderly, which can lead to daytime sedation and anticholinergic adverse events, and patients concomitantly taking other anticholinergic medications (e.g., antidepressants, antipsychotics).[22] Tolerance to sedating effects may develop with daily use.

Various prescription agents are used off-label for their sedating properties. This includes antidepressants, antipsychotics, anxiolytics, anticonvulsants/mood stabilizers, and antihypertensives. This off-label use may be appropriate if there is a comorbidity with an indicated condition such as depression. Issues with use are efficacy for insomnia, safety in insomnia patients, and lack of prescribing guidelines. For example, trazadone is commonly used, even when depression is not a comorbid condition; yet, there is little evidence that it is effective for insomnia. It has a long half-life (10 to 12 hours), so it can lead to daytime sedation, and there can be significant warnings and precautions (suicidal thoughts and behaviors, serotonin syndrome, cardiac arrhythmias, orthostatic hypotension and syncope, increased risk of bleeding, priapism, activation of mania or hypomania, potential for cognitive and motor impairment, angle-closure glaucoma, and hyponatremia).

Current FDA-approved insomnia medications include benzodiazepine receptor agonists (benzodiazepine hypnotics, nonbenzodiazepine hypnotics), a selective melatonin receptor agonist (ramelteon), a selective histamine receptor antagonist (low-dose doxepin), and dual orexin/hypocretin receptor antagonists (suvorexant, lemborexant). Exhibit 4 shows the available brand names, doses, and elimination half-lives.

Benzodiazepine receptor agonist hypnotics are positive allosteric modulators of GABA responses at GABAA receptors. All promote rapid sleep onset. The duration of action of each agent depends upon the dose and elimination half-life; the longer half-life agents can cause residual daytime sleepiness. The FDA added a boxed warning for risks of serious injuries caused by complex sleep behaviors with the nonbenzodiazepines (eszopiclone, zaleplon, and zolpidem) in 2019.[23] Complex sleep behaviors can occur, including sleepwalking, sleep driving, and engaging in other activities when not fully awake. These are rare but have caused serious injuries and deaths. Patients should be advised about the risks, and these agents should be stopped if an episode of complex sleep behavior occurs. All the benzodiazepine receptor agonists may have some abuse liability and are Schedule IV controlled substances.

Ramelteon is a selective melatonin receptor agonist indicated for insomnia with sleep onset difficulty. Interaction at the melatonin one receptor leads to attenuation of the circadian alerting signal

Exhibit 3: Risk Factors for Insomnia

- Comorbid mental and physical disorders
- Temperamental factors
  - Anxiety/worry-prone personality or cognitive style
  - Increased arousal predisposition
  - Tendency to repress emotions
- Environmental
  - Noise
  - Light
  - Uncomfortable temperature
  - High altitude
- Advancing age
- Genetic
  - Female gender: (Females > Males 1.44 to 1)
  - Familial predisposition for disrupted sleep
    - First degree relatives
    - Twins: monozygotic > dizygotic

and at the melatonin two receptor leads to circadian phase reinforcement or shifting. It acts on the suprachiasmatic nucleus and influences the circadian rhythm effects on the sleep-wake cycle. There is no abuse liability with this agent, and it is not a controlled substance.

Low-dose doxepin, an older tricyclic antidepressant, was approved by the FDA in 2010 for the treatment of insomnia characterized by difficulties with sleep maintenance. It is given as an ultra-low dose (3 mg to 6 mg) and has very high histamine H1 selectivity. As with ramelteon, there is no abuse liability, nor controlled substance limitations.

The dual orexin antagonists (DORAs) are the newest class of agents to be approved for insomnia. These are different from older sedative-hypnotics because they reduce wakefulness rather than produce sedation. Orexins are neuropeptides secreted from the lateral hypothalamus neurons. Two orexin neuropeptides, orexin-A and orexin-B, have been identified which act with different affinities on orexin 1 and orexin 2 receptors. Orexin receptors are expressed in many areas of the brain with a suggested role in arousal, appetite, metabolism, reward, stress, and autonomic function. The projections of the orexin system are particularly extensive in the regions of the brain which regulate various aspects of arousal and motivation.

Suvorexant and lemborexant are both indicated for insomnia characterized by difficulties with sleep onset and/or sleep maintenance. The most common adverse event is somnolence and both are Schedule IV controlled substances. Additional single and dual orexin receptor antagonists (SORA and DORA) are in development. Daridorexant, another DORA, was submitted to the FDA for approval in March 2021.

Suvorexant was evaluated in two randomized, double-blind, placebo-controlled, parallel-group, three-month trials in nonelderly (18 to 64 years) and elderly (≥ 65 years) patients with insomnia. Doses of 40 mg and 30 mg (nonelderly/elderly) and 20 mg and 15 mg (nonelderly/elderly) were evaluated. There was an optional three-month, double-blind extension in one trial. Each trial included a one week, randomized, double-blind run-out after double-blind treatment to assess withdrawal/rebound. Efficacy was assessed at week one, month one, and month three by patient-reported subjective total sleep time and time to sleep onset. A subset of patients was evaluated by polysomnography endpoints of wakefulness after persistent sleep onset and latency to onset of persistent sleep (LPS). Suvorexant 40 mg and 30 mg were superior to placebo on all subjective and polysomnography endpoints at night one of week one, month one, and month three in both trials, except for LPS at month three in the second trial.[24] Suvorexant 20 mg and 15 mg were superior to placebo on subjective total sleep time and wakefulness after persistent sleep onset at night one of week one, month one, and month three in both trials and at most individual time points for subjective time to sleep onset and LPS in each trial. Both doses of suvorexant were generally well tolerated, with less than 5 percent of patients discontinuing due to adverse events over three months. The results did not suggest the emergence of marked rebound or withdrawal signs or symptoms when suvorexant was discontinued. A one-year trial of 40 mg (nonelderly) and 30 mg (elderly) also found no emergence of rebound or withdrawals signs or symptoms after one year of continuous use.[25] Although only studied in 62 patients in one of the trials, the FDA-approved dose is 10 mg, no more than once per night taken within 30 minutes of going to bed, with at least seven hours remaining before the planned time of awakening. If the 10 mg dose is well tolerated but not effective, the dose can be increased, not to exceed 20 mg once daily. Higher doses were not approved because of

Exhibit 4: FDA-Approved Insomnia Medications

Generic Name	Brand Name	Available Doses (mg)	Elimination Half-Life (hours)
Benzodiazepine Receptor Agonists			
Benzodiazepines Immediate Release			
Estazolam	ProSom™	1, 2	10 to 24
Flurazepam	Dalmane®	15, 30	2.3 (active metabolite: 48 - 160)
Quazepam	Doral®	7.5, 15	39 (active metabolite 73)
Temazepam	Restoril™	7.5, 15, 22.5, 30	3.5 to 18.4
Triazolam	Halcion®	0.125, 0.25	1.5 to 5.5
Nonbenzodiazepines Immediate Release			
Eszopiclone	Lunesta™	1, 2, 3	~ 6 (~ 9 in elderly)
Zaleplon	Sonata®	5, 10	1
Zolpidem	Ambien®	5, 10	~ 2.5
Nonbenzodiazepines Extended Release			
Zolpidem ER	Ambien CR7	6.25, 12.5	2.8 in males (longer in females)
Nonbenzodiazepines Alternate Delivery			
Zolpidem (oral spray)	Zolpimist®	5, 10	2.7 to 3.0
Zolpidem (sublingual)	Edluar™	5, 10	~ 2.5
Zolpidem (sublingual)	Intermezzo®	1.75, 3.5	~ 2.5
Selective Melatonin Receptor Agonist			
Ramelteon	Rozerem®	8	1 to 2.6
Selective Histamine H_1 Receptor Antagonist			
Doxepin	Silenor®	3, 6	15.3
Dual Orexin Receptor Antagonist			
Lemborexant	Dayvigo™	5, 10	17 to 19
Suvorexant	Belsomra®	5, 10, 15, 20	12

concerns about daytime sleepiness.

Lemborexant 5 mg and 10 mg, zolpidem 6.25 mg, and placebo were compared in subjects 55 and older with insomnia for one month (Sunrise 1). Mean changes from baseline in sleep efficiency at the beginning of therapy (nights 1 and 2) and end of therapy (nights 29 and 30) were significantly larger for both lemborexant doses, compared with placebo ($p < .001$ for both comparisons) and zolpidem ($p < .001$ for both comparisons).[26] The increases in sleep efficiency in both lemborexant treatment groups translated into more than 60 minutes more sleep per night than before treatment. The mean decreases from baseline in wake after sleep onset at the beginning and end of treatment were significantly greater for both doses of lemborexant therapy, compared with placebo and zolpidem ($p < 0.001$). The reduction in time spent awake was observed mostly in the latter half of the sleep period. As measured by polysomnography, both doses of lemborexant therapy reduced wake after sleep onset by more than 45 minutes relative to baseline. Lemborexant 5 mg and 10 mg daily have been shown

Exhibit 5: FDA-Approved Indications

Medication	Unspecified Insomnia	Sleep Onset	Sleep Maintenance	Early Awakening
Estazolam		✓	✓	✓
Flurazepam		✓	✓	✓
Quazepam		✓	✓	✓
Temazepam	✓			
Triazolam	✓			
Eszopiclone		✓	✓	
Zaleplon		✓		
Zolpidem		✓		
Zolpidem ER		✓	✓	
Zolpidem spray		✓		
Zolpidem sublingual		✓		
Zolpidem sublingual-MONT			✓	
Ramelteon		✓		
Low-dose doxepin			✓	
Suvorexant		✓	✓	
Lemborexant		✓	✓	

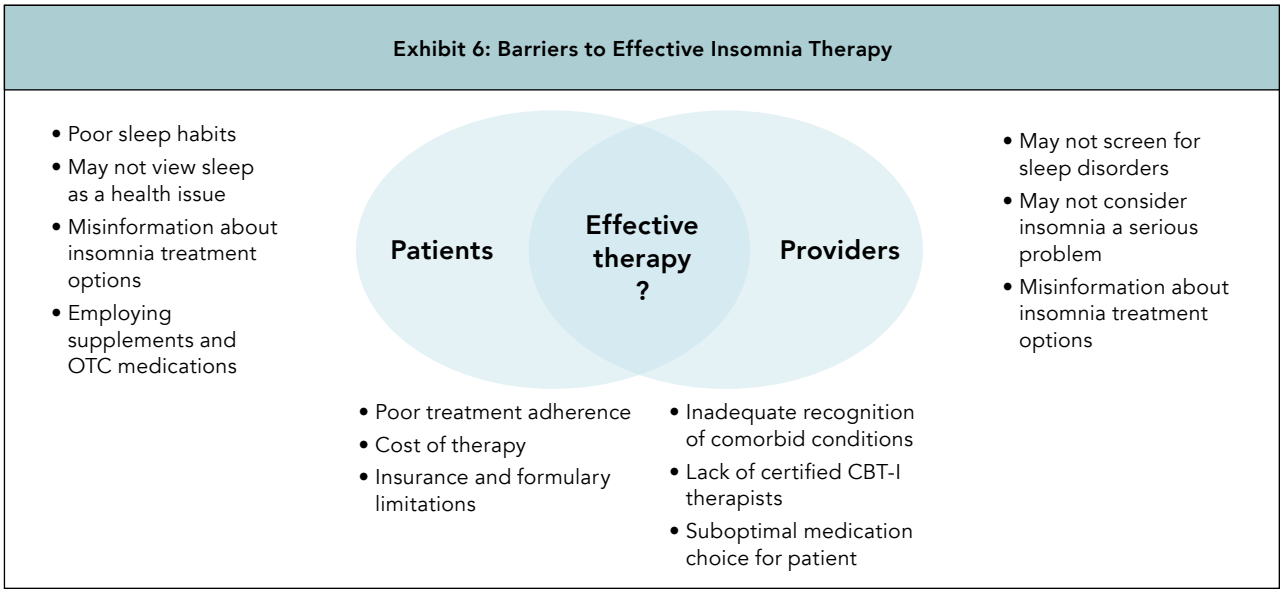
to be effective and safe out to 12 months of use.[27]

The recommended dose of lemborexant is 5 mg taken no more than once per night, immediately before going to bed, with at least seven hours remaining before the planned time of awakening. Dosage may be increased to 10 mg based on clinical response and tolerability. It should be noted that both DORAs are contraindicated in patients with narcolepsy. In addition to patient comorbidities and general health issues, the type of sleep issue can be helpful in selecting therapy. Certain agents are more helpful with sleep onset and others with sleep maintenance (Exhibit 5).

There are many different barriers to effective management of insomnia (Exhibit 6). Poor adherence by patients to healthy sleep habits contributes to poor sleep and undermines resolution of insomnia. Ongoing patient education and better and less expensive ways to deliver CBTi and BBTI may help overcome this barrier. Improper administration of medications occurs frequently which undermines the efficacy of these agents and can increase adverse events. Most prescription directions will specify "bedtime," but this is not well defined for the patient so they take the medication too early or too late before going to bed. Prescribers can prevent some of these issues by educating patients on the correct time to take their medications and the importance of not taking more than prescribed. They can also improve their written instructions on prescriptions by being very precise on timing.

Because the DORAs and other sedative-hypnotics, which are not yet generic, are substantially more expensive than the older generics, such as benzodiazepines and zolpidem, many managed care plans have placed these newer agents in higher co-pay tiers, require step therapy, or require prior authorization. This can limit the use of these appropriate, possibly more effective, and safer agents.

Exhibit 6: Barriers to Effective Insomnia Therapy



Conclusion

Insomnia is a common problem with significant consequences for individuals and society. Health care providers should identify and treat insomnia. Evidence-based treatments include CBT-I and FDA-approved medications. Treatment choices should be personalized for individual patients. New medications target key sleep–wake regulation processes to optimize efficacy and safety.

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When adult patients with obstructive sleep apnea (OSA) or narcolepsy are struggling with excessive daytime sleepiness (EDS),

ONCE-DAILY SUNOSI

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*As seen at week 12.

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WPA=wake-promoting agent.

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INDICATIONS AND USAGE

SUNOSI is indicated to improve wakefulness in adults with excessive daytime sleepiness (EDS) associated with narcolepsy or obstructive sleep apnea (OSA).

Limitations of Use:

SUNOSI is not indicated to treat the underlying obstruction in OSA. Ensure that the underlying airway obstruction is treated (e.g., with continuous positive airway pressure (CPAP)) for at least one month prior to initiating SUNOSI. SUNOSI is not a substitute for these modalities, and the treatment of the underlying airway obstruction should be continued.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

SUNOSI is contraindicated in patients receiving concomitant treatment with monoamine oxidase inhibitors (MAOIs), or within 14 days following discontinuation of an MAOI, because of the risk of hypertensive reaction.

WARNINGS AND PRECAUTIONS

Blood Pressure and Heart Rate Increases

SUNOSI increases systolic blood pressure, diastolic blood pressure, and heart rate in a dose-dependent fashion. Epidemiological data show that chronic elevations in blood pressure increase the risk of major adverse cardiovascular events (MACE), including stroke, heart attack, and cardiovascular death. The magnitude of the increase in absolute risk is dependent on the increase in blood pressure and the underlying risk of MACE in the population being treated. Many patients with narcolepsy and OSA have multiple risk factors for MACE, including hypertension, diabetes, hyperlipidemia, and high body mass index (BMI).

Assess blood pressure and control hypertension before initiating treatment with SUNOSI. Monitor blood pressure regularly during treatment and treat new-onset hypertension and exacerbations of pre-existing hypertension. Exercise caution when treating patients at higher risk of MACE, particularly patients with known cardiovascular and cerebrovascular disease, pre-existing hypertension, and patients with advanced age. Use caution with other drugs that increase blood pressure and heart rate.

Periodically reassess the need for continued treatment with SUNOSI. If a patient experiences increases in blood pressure or heart rate that cannot be managed with dose reduction of SUNOSI or other appropriate medical intervention, consider discontinuation of SUNOSI.

Patients with moderate or severe renal impairment could be at a higher risk of increases in blood pressure and heart rate because of the prolonged half-life of SUNOSI.

Psychiatric Symptoms

Psychiatric adverse reactions have been observed in clinical trials with SUNOSI, including anxiety, insomnia, and irritability.

Exercise caution when treating patients with SUNOSI who have a history of psychosis or bipolar disorders, as SUNOSI has not been evaluated in these patients.

Patients with moderate or severe renal impairment may be at a higher risk of psychiatric symptoms because of the prolonged half-life of SUNOSI.

Observe SUNOSI patients for the possible emergence or exacerbation of psychiatric symptoms. Consider dose reduction or discontinuation of SUNOSI if psychiatric symptoms develop.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5%) reported more frequently with the use of SUNOSI than placebo in either narcolepsy or OSA were headache, nausea, decreased appetite, anxiety, and insomnia.

Please see Brief Summary of full Prescribing Information on next page.

References: 1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders.* 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
2. SUNOSI (solriamfetol) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.

Jazz Pharmaceuticals

SUNOSI® (solriamfetol) tablets, for oral use, CIV
BRIEF SUMMARY OF PRESCRIBING INFORMATION: Consult the Full Prescribing Information for complete product information.
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

SUNOSI is indicated to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA).

Limitations of Use

SUNOSI is not indicated to treat the underlying airway obstruction in OSA. Ensure that the underlying airway obstruction is treated (e.g., with continuous positive airway pressure (CPAP)) for at least one month prior to initiating SUNOSI for excessive daytime sleepiness. Modalities to treat the underlying airway obstruction should be continued during treatment with SUNOSI. SUNOSI is not a substitute for these modalities.

DOSAGE AND ADMINISTRATION

Important Considerations Prior to Initiating Treatment

Prior to initiating treatment with SUNOSI, ensure blood pressure is adequately controlled.

General Administration Instructions

Administer SUNOSI orally upon awakening with or without food. Avoid taking SUNOSI within 9 hours of planned bedtime because of the potential to interfere with sleep if taken too late in the day.

SUNOSI 75 mg tablets are functionally scored tablets that can be split in half (37.5 mg) at the score line.

CONTRAINDICATIONS

SUNOSI is contraindicated in patients receiving concomitant treatment with monoamine oxidase (MAO) inhibitors, or within 14 days following discontinuation of monoamine oxidase inhibitor, because of the risk of hypertensive reaction.

WARNINGS AND PRECAUTIONS

Blood Pressure and Heart Rate Increases

SUNOSI increases systolic blood pressure, diastolic blood pressure, and heart rate in a dose-dependent fashion.

Epidemiological data show that chronic elevations in blood pressure increase the risk of major adverse cardiovascular events (MACE), including stroke, heart attack, and cardiovascular death. The magnitude of the increase in absolute risk is dependent on the increase in blood pressure and the underlying risk of MACE in the population being treated. Many patients with narcolepsy and OSA have multiple risk factors for MACE, including hypertension, diabetes, hyperlipidemia, and high body mass index (BMI).

Assess blood pressure and control hypertension before initiating treatment with SUNOSI. Monitor blood pressure regularly during treatment and treat new-onset hypertension and exacerbations of pre-existing hypertension. Exercise caution when treating patients at higher risk of MACE, particularly patients with known cardiovascular and cerebrovascular disease, pre-existing hypertension, and patients with advanced age. Use caution with other drugs that increase blood pressure and heart rate.

Periodically reassess the need for continued treatment with SUNOSI. If a patient experiences increases in blood pressure or heart rate that cannot be managed with dose reduction of SUNOSI or other appropriate medical intervention, consider discontinuation of SUNOSI.

Patients with moderate or severe renal impairment may be at a higher risk of increases in blood pressure and heart rate because of the prolonged half-life of SUNOSI.

Psychiatric Symptoms

Psychiatric adverse reactions have been observed in clinical trials with SUNOSI, including anxiety, insomnia, and irritability.

SUNOSI has not been evaluated in patients with psychosis or bipolar disorders. Exercise caution when treating patients with SUNOSI who have a history of psychosis or bipolar disorders.

Patients with moderate or severe renal impairment may be at a higher risk of psychiatric symptoms because of the prolonged half-life of SUNOSI.

Patients treated with SUNOSI should be observed for the possible emergence or exacerbation of psychiatric symptoms. If psychiatric symptoms develop in association with the administration of SUNOSI, consider dose reduction or discontinuation of SUNOSI.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Blood Pressure and Heart Rate Increases
- Psychiatric Symptoms

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of SUNOSI has been evaluated in 930 patients (ages 18 to 75 years) with narcolepsy or OSA. Among these patients, 396 were treated with SUNOSI in the 12-week placebo-controlled trials at doses of 37.5 mg (OSA only), 75 mg, and 150 mg once daily. Information provided below is based on the pooled 12-week placebo-controlled studies in patients with narcolepsy or OSA.

Most Common Adverse Reactions

The most common adverse reactions (incidence ≥ 5% and greater than placebo) reported more frequently with the use of SUNOSI than placebo in either the narcolepsy or OSA populations were headache, nausea, decreased appetite, anxiety, and insomnia.

Table 1 presents the adverse reactions that occurred at a rate of ≥ 2% and more frequently in SUNOSI-treated patients than in placebo-treated patients in the narcolepsy population.

Table 1: Adverse Reactions ≥ 2% in Patients Treated with SUNOSI and Greater than Placebo in Pooled 12-Week Placebo-Controlled Clinical Trials in Narcolepsy (75 mg and 150 mg)

	Narcolepsy	
System Organ Class	**Placebo** N = 108 (%)	**SUNOSI** N = 161 (%)
Metabolism and Nutrition Disorders		
Decreased appetite	1	9
Psychiatric Disorders		
Insomnia*	4	5
Anxiety*	1	6
Nervous System Disorders		
Headache*	7	16
Cardiac Disorders		
Palpitations	1	2
Gastrointestinal Disorders		
Nausea*	4	7
Dry mouth	2	4
Constipation	1	3

*"Insomnia" includes insomnia, initial insomnia, middle insomnia, and terminal insomnia. "Anxiety" includes anxiety, nervousness, and panic attack. "Headache" includes headache, tension headache, and head discomfort. "Nausea" includes nausea and vomiting.

Table 2 presents the adverse reactions that occurred at a rate of ≥ 2% and more frequently in SUNOSI-treated patients than in placebo-treated patients in the OSA population.

Table 2: Adverse Reactions ≥ 2% in Patients Treated with SUNOSI and Greater than Placebo in Pooled 12-Week Placebo-Controlled Clinical Trials in OSA (37.5 mg, 75 mg, and 150 mg)

	OSA	
System Organ Class	**Placebo** N = 118 (%)	**SUNOSI** N = 235 (%)
Metabolism and Nutrition Disorders		
Decreased appetite	1	6
Psychiatric Disorders		
Anxiety*	1	4
Irritability	0	3
Nervous System Disorders		
Dizziness	1	2
Cardiac Disorders		
Palpitations	0	3
Gastrointestinal Disorders		
Nausea*	6	8
Diarrhea	1	4
Abdominal pain*	2	3
Dry mouth	2	3
General Disorders and Administration Site Conditions		
Feeling jittery	0	3
Chest discomfort	0	2
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	0	2

*"Anxiety" includes anxiety, nervousness, and panic attack. "Nausea" includes nausea and vomiting. "Abdominal pain" includes abdominal pain, abdominal pain upper, and abdominal discomfort.

Other Adverse Reactions Observed During the Premarketing Evaluation of SUNOSI

Other adverse reactions of < 2% incidence but greater than placebo are shown below. The following list does not include adverse reactions: 1) already listed in previous tables or elsewhere in the labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, or 4) which were not considered to have clinically significant implications.

Narcolepsy population:

Psychiatric disorders: agitation, bruxism, irritability

Respiratory, thoracic and mediastinal disorders: cough

Skin and subcutaneous tissue disorders: hyperhidrosis

General disorders and administration site conditions: feeling jittery, thirst, chest discomfort, chest pain

Investigations: weight decreased

OSA population

Psychiatric disorders: bruxism, restlessness

Nervous system disorders: disturbances in attention, tremor

Respiratory, thoracic and mediastinal disorders: cough, dyspnea

Gastrointestinal disorders: constipation, vomiting

Investigations: weight decreased

Dose-Dependent Adverse Reactions

In the 12-week placebo-controlled clinical trials that compared doses of 37.5 mg, 75 mg, and 150 mg daily of SUNOSI to placebo, the following adverse reactions were dose-related: headache, nausea, decreased appetite, anxiety, diarrhea, and dry mouth (Table 3).

Table 3: Dose-Dependent Adverse Reactions ≥ 2% in Patients Treated with SUNOSI and Greater than Placebo in Pooled 12-Week Placebo-Controlled Clinical Trials in Narcolepsy and OSA

	Placebo N = 226 (%)	**SUNOSI 37.5 mg** N = 58* (%)	**SUNOSI 75 mg** N = 120 (%)	**SUNOSI 150 mg** N = 218 (%)
Headache**	8	7	9	13
Nausea**	5	7	5	9
Decreased appetite	1	2	7	8
Anxiety	1	2	3	7
Dry mouth	2	2	3	4
Diarrhea	2	2	4	5

*In OSA only.

**"Headache" includes headache, tension headache, and head discomfort. "Nausea" includes nausea and vomiting.

Adverse Reactions Resulting in Discontinuation of Treatment

In the 12-week placebo-controlled clinical trials, 11 of the 396 patients (3%) who received SUNOSI discontinued because of an adverse reaction compared to 1 of the 226 patients (< 1%) who received placebo. The adverse reactions resulting in discontinuation that occurred in more than one SUNOSI-treated patient and at a higher rate than placebo were: anxiety (2/396; < 1%), palpitations (2/396; < 1%), and restlessness (2/396; < 1%).

Increases in Blood Pressure and Heart Rate

SUNOSI's effects on blood pressure and heart rate are summarized below. Table 4 shows maximum mean changes in blood pressure and heart rate recorded at sessions where the Maintenance of Wakefulness Test (MWT) was administered. Table 5 summarizes 24-hour ambulatory blood pressure monitoring (ABPM) and ambulatory heart rate monitoring performed in the outpatient setting.

Table 4: Maximal Mean Changes in Blood Pressure and Heart Rate Assessed at MWT Sessions from Baseline through Week 12: Mean (95% CI)*

		Placebo	SUNOSI 37.5 mg	SUNOSI 75 mg	SUNOSI 150 mg	SUNOSI 300 mg**
Narcolepsy *STUDY 1*	n	52		51	49	53
	SBP	3.5 (0.7, 6.4)	-	3.1 (0.1, 6.0)	4.9 (1.7, 8.2)	6.8 (3.2, 10.3)
	n	23		47	49	53
	DBP	1.8 (-1.8, 5.5)	-	2.2 (0.2, 4.1)	4.2 (2.0, 6.5)	4.2 (1.5, 6.9)
	n	48		26	49	53
	HR	2.3 (-0.1, 4.7)	-	3.7 (0.4, 6.9)	4.9 (2.3, 7.6)	6.5 (3.9, 9.0)
OSA *STUDY 2*	n	35	17	54	103	35
	SBP	1.7 (-1.4, 4.9)	4.6 (-1.1, 10.2)	3.8 (1.2, 6.4)	2.4 (0.4, 4.4)	4.5 (1.1, 7.9)
	n	99	17	17	107	91
	DBP	1.4 (-0.1, 2.9)	1.9 (-2.3, 6.0)	3.2 (-0.9, 7.3)	1.8 (0.4, 3.2)	3.3 (1.8, 4.8)
	n	106	17	51	102	91
	HR	1.7 (0.1, 3.3)	1.9 (-1.9, 5.7)	3.3 (0.6, 6.0)	2.9 (1.4, 4.4)	4.5 (3.0, 6.0)

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate

*For study weeks 1, 4, and 12, SBP, DBP, and HR were assessed pre-dose and every 1-2 hours for 10 hours after test drug administration. For all time points at all visits, the mean change from baseline was calculated, by indication and dose, for all patients with a valid assessment. The table shows, by indication and dose, the mean changes from baseline for the week and time point with the maximal change in SBP, DBP, and HR.

**The maximum recommended daily dose is 150 mg. Dosages above 150 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

Table 5: Blood Pressure and Heart Rate by 24-hour Ambulatory Monitoring: Mean Change (95% CI) from Baseline at Week 8

		Placebo	SUNOSI 37.5 mg	SUNOSI 75 mg	SUNOSI 150 mg	SUNOSI 300 mg**
Narcolepsy *STUDY 1*	n*	46		44	44	40
	SBP	-0.4 (-3.1, 2.4)	-	1.6 (-0.4, 3.5)	-0.5 (-2.1, 1.1)	2.4 (0.5, 4.3)
	DBP	-0.2 (-1.9, 1.6)	-	1.0 (-0.4, 2.5)	0.8 (-0.4, 2.0)	3.0 (1.4, 4.5)
	HR	0.0 (-1.9, 2.0)	-	0.2 (-2.1, 2.4)	1.0 (-1.2, 3.2)	4.8 (2.3, 7.2)
OSA *STUDY 2*	n*	92	43	49	96	84
	SBP	-0.2 (-1.8, 1.4)	1.8 (-1.1, 4.6)	2.6 (0.02, 5.3)	-0.2 (-2.0, 1.6)	2.8 (-0.1, 5.8)
	DBP	0.2 (-0.9, 1.3)	1.4 (-0.4, 3.2)	1.5 (-0.04, 3.1)	-0.1 (-1.1, 1.0)	2.4 (0.5, 4.4)
	HR	-0.4 (-1.7, 0.9)	0.4 (-1.4, 2.2)	1.0 (-0.9, 2.81)	1.7 (0.5, 2.9)	1.6 (0.3, 2.9)

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate

*Number of patients who had at least 50% valid ABPM readings.

**The maximum recommended daily dose is 150 mg. Dosages above 150 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

DRUG INTERACTIONS

Monoamine Oxidase (MAO) Inhibitors

Do not administer SUNOSI concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment. Concomitant use of MAO inhibitors and noradrenergic drugs may increase the risk of a hypertensive reaction. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.

Drugs that Increase Blood Pressure and/or Heart Rate

Concomitant use of SUNOSI with other drugs that increase blood pressure and/or heart rate has not been evaluated, and such combinations should be used with caution.

Dopaminergic Drugs

Dopaminergic drugs that increase levels of dopamine or that bind directly to dopamine receptors might result in pharmacodynamic interactions with SUNOSI. Interactions with dopaminergic drugs have not been evaluated with SUNOSI. Use caution when concomitantly administering dopaminergic drugs with SUNOSI.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SUNOSI during pregnancy. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling 1-877-283-6220 or contacting the company at *www.SunosiPregnancyRegistry.com*.

Risk Summary

Available data from case reports are not sufficient to determine drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproductive studies, oral administration of solriamfetol during organogenesis caused maternal and fetal toxicities in rats and rabbits at doses ≥ 4 and 5 times and was teratogenic at doses 19 and ≥ 5 times, respectively, the maximum recommended human dose (MRHD) of 150 mg based on mg/m^2 body surface area. Oral administration of solriamfetol to pregnant rats during pregnancy and lactation at doses ≥ 7 times the MRHD based on mg/m^2 body surface area resulted in maternal toxicity and adverse effects on fertility, growth, and development in offspring *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Solriamfetol was administered orally to pregnant rats during the period of organogenesis at 15, 67, and 295 mg/kg/day, which are approximately 1, 4, and 19 times the MRHD based on mg/m^2 body surface area. Solriamfetol at ≥ 4 times the MRHD caused maternal toxicity that included hyperactivity, significant decreases in body weight, weight gain, and food consumption. Fetal toxicity at these maternally toxic doses included increased incidence of early resorption and post-implantation loss, and decreased fetal weight.

Solriamfetol was teratogenic at 19 times the MRHD; it increased the incidence of fetal malformations that included severe sternebrae mal-alignment, hindlimb rotation, bent limb bones, and situs inversus. This dose was also maternally toxic. The no-adverse-effect level for malformation is 4 times and for maternal and embryofetal toxicity is approximately 1 times the MRHD based on mg/m^2 body surface area.

Solriamfetol was administered orally to pregnant rabbits during the period of organogenesis at 17, 38, and 76 mg/kg/day, which are approximately 2, 5, and 10 times the MRHD based on mg/m^2 body surface area. Solriamfetol at 10 times the MRHD caused maternal toxicity of body weight loss and decreased food consumption. Solriamfetol was teratogenic at ≥ 5 times the MRHD, it caused fetal skeletal malformation (slight-to-moderate sternebrae mal-alignment) and decreased fetal weight. The no-adverse-effect level for malformation and fetal toxicity is approximately 2 times and for maternal toxicity is approximately 5 times the MRHD based on mg/m^2 body surface area.

Solriamfetol was administered orally to pregnant rats during the period of organogenesis from gestation day 7 through lactation day 20 post-partum, at 35, 110, and 350 mg/kg/day, which are approximately 2, 7, and 22 times the MRHD based on mg/m^2 body surface area. At ≥ 7 times the MRHD, solriamfetol caused maternal toxicity that included decreased body weight gain, decreased food consumption, and hyperpnea. At these maternally toxic doses, fetal toxicity included increased incidence of stillbirth, postnatal pup mortality, and decreased pup weight. Developmental toxicity in offspring after lactation day 20 included decreased body weight, decreased weight gain, and delayed sexual maturation. Mating and fertility of offspring were decreased at maternal doses 22 times the MRHD without affecting learning and memory. The no-adverse-effect level for maternal and developmental toxicity is approximately 2 times the MRHD based on mg/m^2 body surface area.

LACTATION

Risk Summary

There are no data available on the presence of solriamfetol or its metabolites in human milk, the effects on the breastfed infant, or the effect of this drug on milk production.

Solriamfetol is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUNOSI and any potential adverse effects on the breastfed child from SUNOSI or from the underlying maternal condition.

Clinical Considerations

Monitor breastfed infants for adverse reactions, such as agitation, insomnia, anorexia and reduced weight gain.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of SUNOSI in pediatric patients have not been conducted.

Geriatric Use

Of the total number of patients in the narcolepsy and OSA clinical studies treated with SUNOSI, 13% (123/930) were 65 years of age or over.

No clinically meaningful differences in safety or effectiveness were observed between elderly and younger patients.

Solriamfetol is predominantly eliminated by the kidney. Because elderly patients are more likely to have decreased renal function, dosing may need to be adjusted based on eGFR in these patients. Consideration should be given to the use of lower doses and close monitoring in this population.

Renal Impairment

Dosage adjustment is not required for patients with mild renal impairment (eGFR 60-89 mL/min/1.73 m^2). Dosage adjustment is recommended for patients with moderate to severe renal impairment (eGFR 15-59 mL/min/1.73 m^2). SUNOSI is not recommended for patients with end stage renal disease (eGFR <15 mL/min/1.73 m^2).

DRUG ABUSE AND DEPENDENCE

Controlled Substance

SUNOSI contains solriamfetol, a Schedule IV controlled substance.

Abuse

SUNOSI has potential for abuse. Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. The abuse potential of SUNOSI 300 mg, 600 mg, and 1200 mg (two, four, and eight times the maximum recommended dose, respectively) was assessed relative to phentermine, 45 mg and 90 mg, (a Schedule IV controlled substance) in a human abuse potential study in individuals experienced with the recreational use of stimulants. Results from this clinical study demonstrated that SUNOSI produced Drug Liking scores similar to or lower than phentermine. In this crossover study, elevated mood was reported by 2.4% of placebo-treated subjects, 8 to 24% of SUNOSI-treated subjects, and 10 to 18% of phentermine-treated subjects. A 'feeling of relaxation' was reported in 5% of placebo-treated subjects, 5 to 19% of SUNOSI-treated subjects and 15 to 20% of phentermine-treated subjects.

Physicians should carefully evaluate patients for a recent history of drug abuse, especially those with a history of stimulant (e.g., methylphenidate, amphetamine, or cocaine) or alcohol abuse, and follow such patients closely, observing them for signs of misuse or abuse of SUNOSI (e.g., incrementation of doses, drug-seeking behavior).

Dependence

In a long-term safety and maintenance of efficacy study, the effects of abrupt discontinuation of SUNOSI were evaluated following at least 6 months of SUNOSI use in patients with narcolepsy or OSA. The effects of abrupt discontinuation of SUNOSI were also evaluated during the two-week safety follow-up periods in the Phase 3 studies. There was no evidence that abrupt discontinuation of SUNOSI resulted in a consistent pattern of adverse events in individual subjects that was suggestive of physical dependence or withdrawal.

OVERDOSAGE

A specific reversal agent for SUNOSI is not available. Hemodialysis removed approximately 21% of a 75 mg dose in end stage renal disease patients. Overdoses should be managed with primarily supportive care, including cardiovascular monitoring.

Consult with a Certified Poison Control Center at 1-800-222-1222 for latest recommendations.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Potential for Abuse and Dependence

Advise patients that SUNOSI is a federally controlled substance because it has the potential to be abused. Advise patients to keep their medication in a secure place and to dispose of unused SUNOSI as recommended in the Medication Guide.

Primary OSA Therapy Use

Inform patients that SUNOSI is not indicated to treat the airway obstruction in OSA and they should use a primary OSA therapy, such as CPAP, as prescribed to treat the underlying obstruction. SUNOSI is not a substitute for primary OSA therapy.

Blood Pressure and Heart Rate Increases

Instruct patients that SUNOSI can cause elevations of their blood pressure and pulse rate and that they should be monitored for such effects.

Psychiatric Symptoms

Instruct patients to contact their healthcare provider if they experience, anxiety, insomnia, irritability, agitation, or signs of psychosis or bipolar disorders.

Lactation

Monitor breastfed infants for adverse reactions such as agitation, insomnia, anorexia, and reduced weight gain.

For more information, visit www.SUNOSI.com

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Best Practices in the Treatment and Management of Cystic Fibrosis: Recent Updates and Advances in CFTR Therapy

Patrick A. Flume, MD

For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

The genetic mutations which cause cystic fibrosis (CF) are known and can now be targeted with oral therapies which decrease the symptoms and complications of the disease. Most CF patients in the United States (U.S.) are eligible for these therapies and should be started on them as early in life as possible.

Key Points

- CFTR modulation is changing outcomes in CF.
- These therapies are available for most patients, and the treatment selection depends on the genetic mutations present.
- Additional therapies are on the horizon.

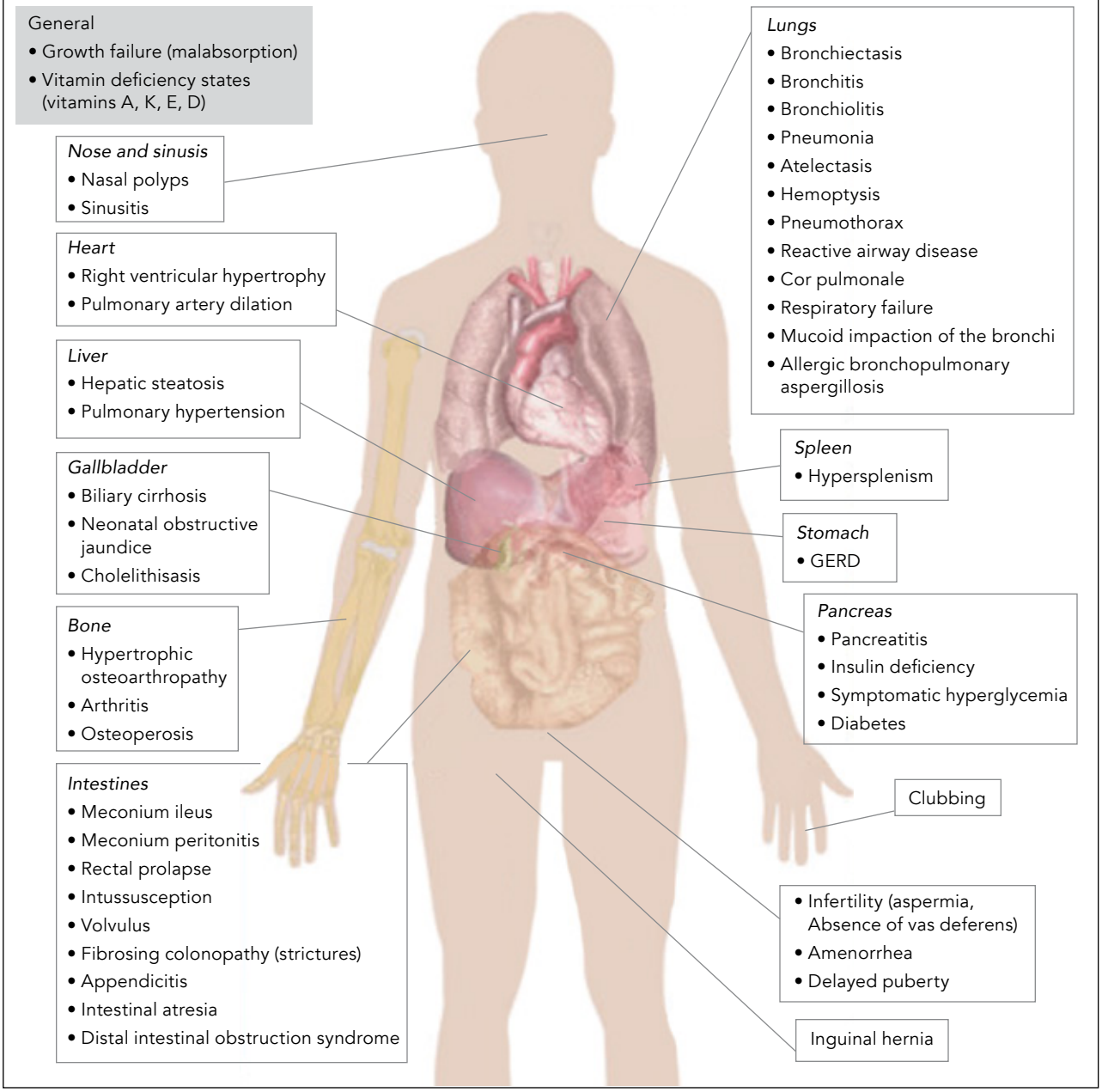
CYSTIC FIBROSIS (CF) IS AN AUTOSOMAL recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Greater than 2,000 mutations in the CFTR gene have been reported, but only 25 mutations are found in most patients.[1] The dysfunctional CFTR protein produced by the CFTR mutations results in thick, sticky mucus that obstructs the airways and ducts of the pancreas and liver. Virtually every organ can be impacted either primarily or secondarily by the disease (Exhibit 1). Respiratory failure is the primary cause of death in CF.

Survival of the patient with CF has improved significantly from five years or less in the 1940s to 46 years in 2015 to 2019, and there are now more adults living with CF than there are children with the disease.[2] Treatments of the downstream consequences of the disease, including airway clearance techniques, nutritional support with pancreatic enzymes, inhaled antibiotics, and oral antibiotics, have driven much of the survival benefit. Survival improvements will continue to be seen with the use of CFTR targeting medications which target the underlying pathology and were first approved in 2012.

CFTR mutations can be categorized into five different classes which are grouped by the issues in the production of the CFTR protein.[3] The amount of functional CFTR activity is closely correlated with disease severity (Exhibit 2). Class I are protein production mutations, Class II are protein processing mutations, Class III are gating mutations, Class IV are conduction mutations, and Class V are insufficient protein mutations.[1,3] Class IV and V mutations are residual function mutations, and the population with these mutations tend to have less severe disease. The final type of mutation (Class VI) can result in a working CFTR protein; however, the protein configuration is not stable and will degrade too quickly once on the cell surface. F508del, a Class II mutation that results in defective processing but also causes a gating issue, is the most common mutation in CF patients in the U.S. Forty-four percent of CF patients are homozygous F508del and 40 percent are heterozygous.[2] The mutations a patient with CF has must be known to select therapy.

Correctors and potentiators are two ways to increase CFTR function that have already reached

Exhibit 1: Manifestations of Cystic Fibrosis

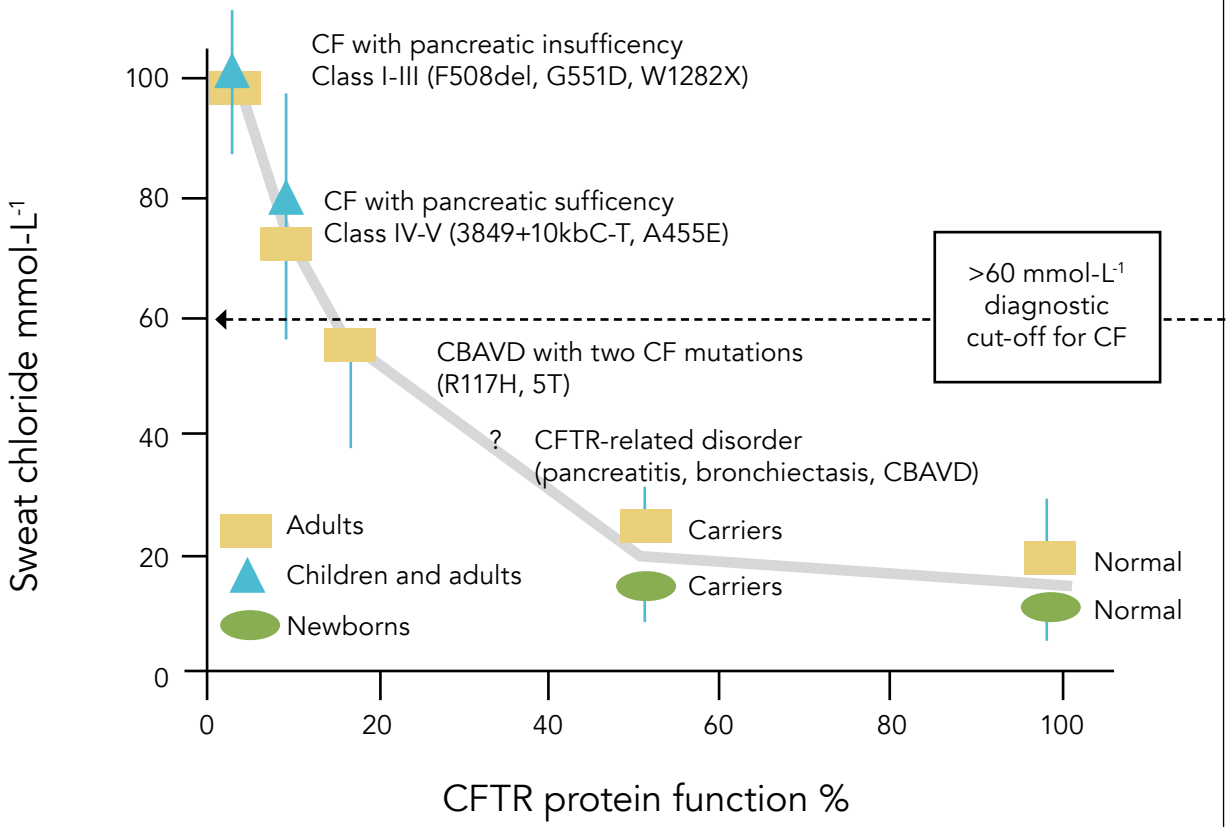


the market (Exhibit 3). Correctors increase the cellular processing and delivery of CFTR proteins to the cell surface and potentiators increase the flow of ions through CFTR present on the cell surface.

Ivacaftor (Kalydeco®) is a potentiator and was the first disease-modifying agent approved for CF. It is indicated for the treatment of CF in patients aged six months and older who have at least one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data. This includes the G551D mutation, other gating mutations, and residual function (Class IV and V) mutations, which is about 14 percent of the total CF population.[4] It is not effective as monotherapy for those who with homozygous F508del mutation, but it does work in combination with correctors.[5]

Ivacaftor increases lung function about 12 percent, decreases chloride content in sweat to almost normal values, and decreases the rate of lung function decline in patients with appropriate mutations by about 50 percent.[6-10] Ivacaftor also reduces pulmonary exacerbation rates, even in

Exhibit 2: Impact of Gene Mutations on CFTR Protein Function



those whose lung function does not improve.[11] U.S. registry data, from the first three years after approval, found that ivacaftor-treated patients had significantly lower risks of death (0.6% versus 1.6%, $p = 0.0110$), transplantation (0.2% versus 1.1%, $p = 0.0017$), hospitalization (27.5% versus 43.1%, $p < 0.0001$) and pulmonary exacerbation (27.8% versus 43.3%, $p < 0.0001$) relative to those not treated with ivacaftor (because they had different CFTR mutations).[12]

Three correctors are now FDA-approved: lumacaftor, tezacaftor, and elexacaftor. These are given in combination products which also contain ivacaftor because a corrector alone was found to not change CFTR function sufficiently. Lumacaftor/ivacaftor (Orkambi®) is FDA-approved for treating patients aged two years and older who are homozygous for the F508del mutation in the CFTR gene. Tezacaftor/ivacaftor (Symdeko®) is FDA-approved for those aged six and older who are F508del homozygous or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence. Triple combination therapy with two correctors that work differently and a potentiator [elexacaftor/tezacaftor/ivacaftor (Trikafta®)] was FDA-approved in October 2019 for patients aged 12 years and older who have at least one F508del mutation in the CFTR gene or a CFTR mutation that is responsive based on in vitro data. The triple combination has become the most used combination for those with appropriate mutations (~ 85% of CF population) because of effectiveness in correcting the CFTR function (Exhibit 4).

Triple combination therapy results in improvements in respiratory function, pulmonary exacerbation rates, hospitalizations, and lung function decline.[13,14] A 60 percent reduction in loss of lung function can be seen which shows that CFTR modulation is altering the disease outcome. Additional benefits of CFTR modulation include improved quality of life scores, improved weight gain, increased fecal elastase (which may indicate preservation of pancreatic exocrine function), reduction in sinus complications, reduced need for insulin for glycemic control, and improved female fertility. The Medical

Exhibit 3: Approaches to Increasing CFTR Activity

- Increase the opening time of CFTR protein resulting in greater ion flow
  - Potentiators (ivacaftor)
- Facilitate processing and trafficking of CFTR protein
  - Correctors (lumacaftor, tezacaftor, and elexacaftor)
- Prolong presence of CFTR protein
  - GSNOR inhibitors*
- Increase the amount of immature CFTR protein
  - Gene therapy*
  - DNA editing*
  - mRNA editing*
  - Read-through premature stop codons*
  - Amplifiers (increased translation)*

* Investigational areas

University of South Carolina Cystic Fibrosis Center has seen about a fivefold increase in pregnancies in their patients treated with CFTR modulation.

The right candidates for CFTR modulation are any patient with CF with an appropriate mutation (ignoring age and lung function). For rare mutations not included in labeling, if there is a reasonable expectation of response or laboratory data that predict response, then CFTR modulation would be appropriate. CF centers can conduct laboratory testing with an individual patient's cells to show response to therapy. Those who are not candidates for CFTR modulators include those unwilling or unable to comply with periodic monitoring (liver function and pulmonary function testing) or with previously demonstrated intolerance to the therapies. Severe liver disease is not an absolute contraindication but requires dosage change and closer monitoring. Concomitant medications which interfere with the CFTR modulators require dosage changes or a medication change if possible.

In patients, clinicians are seeing improved lung function like what was seen in clinical trials. Improvements are highly variable, with some increasing ~ 5 percent and others as much as 50 percent. Patients have a marked reduction in cough and sputum production; this is a tradeoff that makes it more difficult to monitor respiratory cultures. These agents are reasonably well tolerated, although some patients do stop them because of headaches, fatigue with increased creatinine phosphokinase levels, and weight loss.

There are still some ongoing issues with CFTR modulation that need to be resolved. Studies of triple combination therapy in those less than 12 years of age are currently ongoing; however, it will be while before it is approved for the youngest patients. Ideally, therapy could be started very young to prevent any lung or other organ damage. There are still those patients who do not benefit from current modulators, those who cannot tolerate approved products, and those whose mutations are not responsive. More options are still needed.

Another issue is what to do about all the currently used background therapies that treat the downstream effects of CF. Patients would like to reduce their treatment burden, which is substantial between all the oral medications, inhaled medications, and physical therapies. All the modulators were studied in combination with background therapies. Those with structural lung disease (bronchiectasis) are still likely to have impaired mucociliary clearance and persistent infection despite CFTR modulation and will need to continue background therapies. SIMPLIFY is a planned withdrawal study to assess safety of cessation of dornase and hypertonic saline. Although CFTR modulation is not a cure for CF, for children started on CFTR modulators very early, they likely will not need as many background therapies.

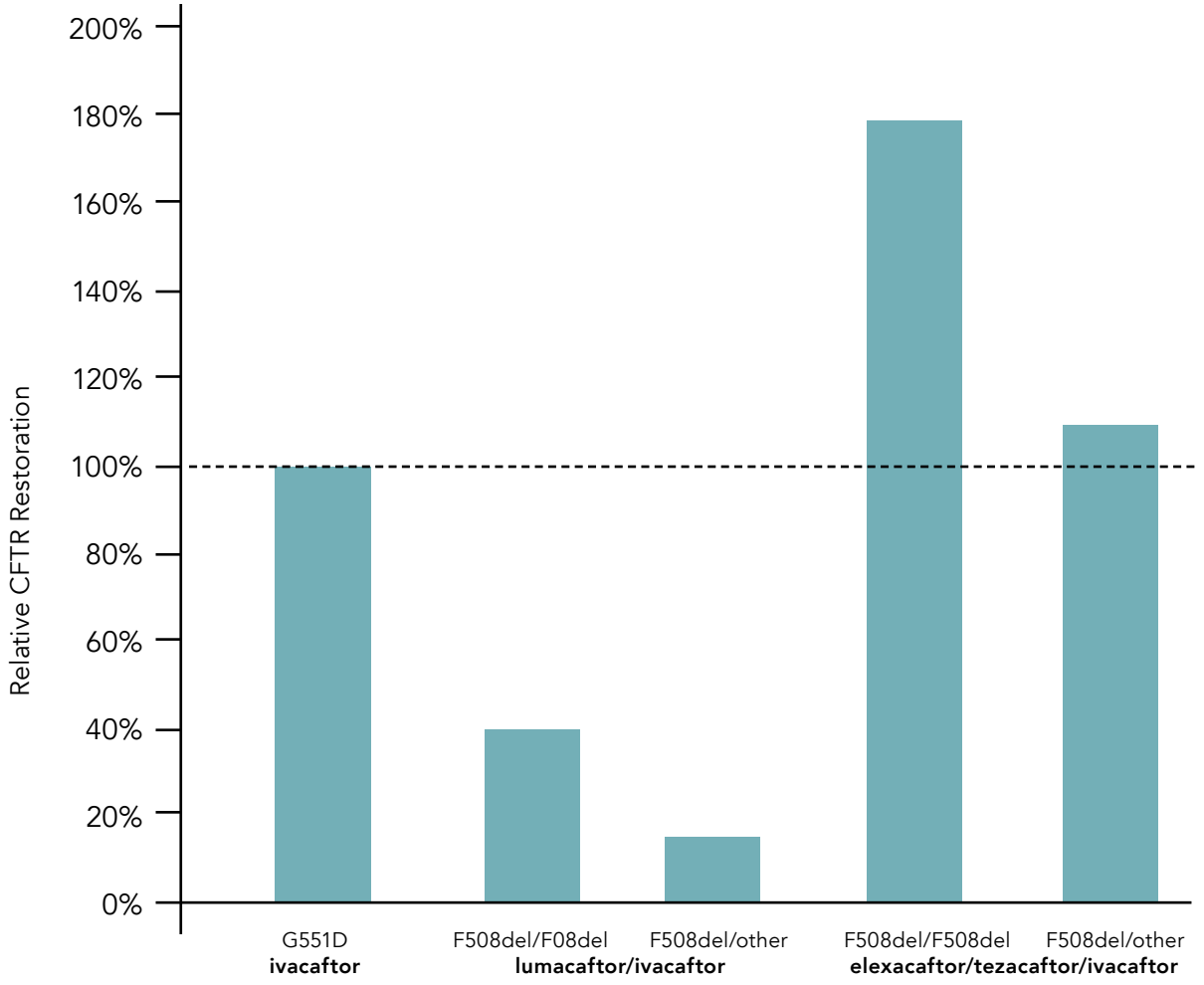
A last issue is how to treat those who are diagnosed with CF as adults. These patients typically have modestly abnormal sweat chloride, milder respiratory impairment, better preserved lung function, less severe bronchiectasis, and preserved pancreatic function. They may get identified as having CF because of persistent infections with unusual organisms such as *pseudomonas* or *mycobacteria*, or because of infertility. Deciding to treat will require a discussion between the patient and a CF specialist.

Early intervention with the most effective therapies is the best approach in optimizing outcomes in CF. Because of the treatment burden, clinicians should use a partnered approach to enhance adherence utilizing various team members (dietitian, respiratory therapist, pharmacist, social worker, psychologist). CF centers are working on novel methods to deliver interdisciplinary care models, increased use of telemedicine, increased use of home devices (spirometers, scales) to monitor care, enhanced use of other technologies (e.g., smartphones monitoring step count, symptoms), and best ways to monitor for respiratory infections.

Conclusion

CFTR modulators are dramatically changing the outcomes of CF but are not a cure. Long-term

Exhibit 4: Benefit of Triple Therapy



100% is not "normal," but relative to benefit of ivacaftor in G551D mutated CF

benefits such as a reduction in lung transplants and death from CF are already being seen. It will be interesting to see the impact of starting CFTR modulator therapy at an early age on the natural history of the disease. Additional therapies which might even be cures are on the horizon.

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Novel Treatment Advances and Approaches in the Management of Type 2 Diabetes: A Closer Look at the Evolving Role of SGLT2 Inhibitors

Jennifer B. Green, MD

For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

Although cardiovascular and kidney disease are well known complications of diabetes, the use of guideline-directed therapies which reduce these risks are seriously suboptimal. Increasing use of the diabetes medications, along with antihypertensives and lipid-lowering therapies, will reduce risk and should be a goal for providers and managed care.

Key Points

- Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP-1 RA) classes of diabetes medications have significant benefit in reducing risk of recurrent atherosclerotic cardiovascular disease (ASCVD) events, heart failure (HF) hospitalizations, and cardiovascular disease (CVD) mortality.
- These agents are recommended additions to metformin therapy for certain patient groups, regardless of the need for additional glucose lowering.
- Improving use of guideline-recommended therapies including SGLT2i and GLP-1 RA is an important opportunity for managed care to improve overall diabetes care.

SOME 425 MILLION PEOPLE WORLDWIDE, or 8.8 percent of adults 20 to 79 years of age, are estimated to have diabetes.[1] Approximately 79 percent live in low- and middle-income countries. Despite "good" control of glucose, blood pressure, and lipids, patients with type 2 diabetes mellitus (T2DM) are still dying of cardiovascular disease (CVD). CVD occurs earlier, with greater severity, and with more diffuse distribution than in those without DM. Two-thirds of deaths in T2DM are attributable to CVD. Approximately 40 percent are from ischemic heart disease, 15 percent from other forms of heart disease, principally heart failure, and 10 percent from stroke.[2] A 50-year-old with diabetes dies, on average, six years earlier than a counterpart without diabetes, with about 60 percent of the difference in survival attributable to excess vascular deaths.[3] The impact of DM on CVD development begins many years before diagnosis.

Numerous interventions have been shown to reduce the risk of CVD in those with DM. Intensive management of hemoglobin A1C (A1C), blood pressure, and lipids reduced risk of micro and macrovascular complications – using older drugs – by about 50 percent.[4] The rates of certain serious complications from T2DM fell from 1990 to 2010, but the number of events did not, likely due to increasing numbers of people with T2DM.[5] The largest relative declines were in acute myocardial infarction (-67.8%) and death from hyperglycemic crisis (-64.4%), followed by stroke and amputations, which each declined by approximately half (-52.7%

Exhibit 1: MACE Effect of Newer Classes[6-17]

Drug Class	SAVOR TIMI-53 saxagliptin	EXAMINE alogliptin	TECOS sitagliptin	CARMELINA linagliptin	
DPP-4 inhibitor	Neutral	Neutral	Neutral	Neutral	
	LEADER liraglutide	ELIXA lixisenatide	SUSTAIN-6 semaglutide injection	EXSCEL exenatide once weekly	REWIND dulaglutide
GLP-1 agonist	Beneficial	Neutral	Beneficial	Neutral	Beneficial
	EMPA-REG empagliflozin	CANVAS canagliflozin	DECLARE dapagliflozin		
SGLT2 inhibitor	Beneficial	Beneficial	Neutral		

MACE = Major adverse cardiovascular events (usually CV death, myocardial infarction, and stroke).
All trials listed enrolled patients with type 2 diabetes and established atherosclerotic CV disease, or multiple risk factors for the same.
REWIND enrolled a majority of patients with multiple risk factors rather than established ASCVD.
DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide one; SGLT2 = sodium-glucose cotransporter-2

and -51.4%), with the smallest decline being end-stage renal disease (-28.3%; 95% CI, -34.6 to -21.6). When expressed as rates for the overall population, in which a change in prevalence also affects complication rates, there was a decline in rates of acute myocardial infarction and death from hyperglycemic crisis (2.7 and 0.1 fewer cases per 10,000, respectively), but not in rates of amputation, stroke, or end-stage renal disease (ESRD). Despite these advances, a large burden of disease persists because of the continued increase in the prevalence of T2DM.

There are now numerous medications for managing glycemic control. Since 2008, manufacturers must evaluate new antiglycemic products for their effects on CVD. Those that show benefit can carry specific labeling on CVD benefits. Twenty-four of these CVD risk studies have been published. Exhibits 1 and 2 outline the findings from trials with the three newest classes – dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon like peptide 1 receptor antagonists (GLP-1 RA), and sodium-glucose cotransporter-2 inhibitors (SGLT2i).[6-17] In general the DPP-4i have been found to be neutral in terms of major adverse cardiovascular events [usually CV death, myocardial infarction, and stroke; major adverse cardiovascular events (MACE)] and heart failure (HF). They neither increase nor decrease events except for saxagliptin and HF. Of the GLP-1 RA, liraglutide, semaglutide, and dulaglutide have been shown to reduce MACE and all are neutral in terms of HF.

Delving further into the SGLT2i, these agents lower blood glucose by inhibiting SGLT2, which is expressed in the proximal renal tubules and accounts for about 90 percent of the reabsorption of glucose from tubular fluid. SGLT2i work independently of insulin and lead to negative energy balance by enhanced urinary glucose excretion. Consequently, they promote weight loss and do not induce hypoglycemia. Along with the primary antihyperglycemic effect, SGLT2i possess multidimensional properties that may favorably influence CVD and kidney disease prognosis (Exhibit 3).[18] The most recent meta-analysis of the CVD trials concluded that SGLT2i protect against CVD and death in diverse subsets of patients with T2DM, regardless of cardiovascular disease history.[19]

In the trials to date, patients treated with SGLT2i had reduced progression of albuminuria and less decline in estimated glomerular filtration rate (eGFR) over time compared to placebo. SGLT2i therapy also reduces risks of progression to ESRD or death in patients with T2DM and atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease CKD.[19-22] The CV benefit with SGLT2i therapy may be greater in patients with lower eGFR.[21]

Diabetes, CKD, and HF are closely associated, common conditions. Diabetes increases risk for

Exhibit 2: Heart Failure Effect of Newer Classes[6-17]

Drug Class	SAVOR TIMI-53 saxagliptin	EXAMINE alogliptin	TECOS sitagliptin	CARMELINA linagliptin	
DPP-4 inhibitor	Increased Risk	Neutral	Neutral	Neutral	
	LEADER liraglutide	ELIXA lixisenatide	SUSTAIN-6 semaglutide injection	EXSCEL exenatide once weekly	REWIND dulaglutide
GLP-1 agonist	Neutral	Neutral	Neutral	Neutral	Neutral
	EMPA-REG empagliflozin	CANVAS canagliflozin	DECLARE dapagliflozin	DAPA HF dapagliflozin	
SGLT2 inhibitor	Beneficial	Beneficial	Beneficial	Beneficial	

All trials listed other than DAPA-HF enrolled patients with type 2 diabetes and established atherosclerotic CV disease, or multiple risk factors for the same. HF endpoints in most trials were hospitalizations due to heart failure. DAPA-HF enrolled patients with heart failure (HF) with reduced ejection fraction with or without diabetes. Primary outcome was worsening HF event or cardiovascular death (worsening HF event = unplanned HF hospitalization or an urgent heart failure visit requiring intravenous therapy).

both and CKD patients are at increased risk for HF. Patients with diabetes and HF or CKD have worse outcomes. HF is a leading cause of CVD among patients with CKD and ESRD.[23] Almost 30 percent of Medicare patients with CKD also have HF, compared with 6 percent of Medicare patients without CKD. Risk of incident HF is three times greater in individuals with an eGFR < 60 mL/min/1.73m^2 compared with those with eGFR > 90. HF with preserved ejection fraction (HFpEF) is more common than HF with reduced ejection fraction (HFrEF) in patients with CKD.[24] DM, CKD, and HF, especially when combined, have significant public health implications.

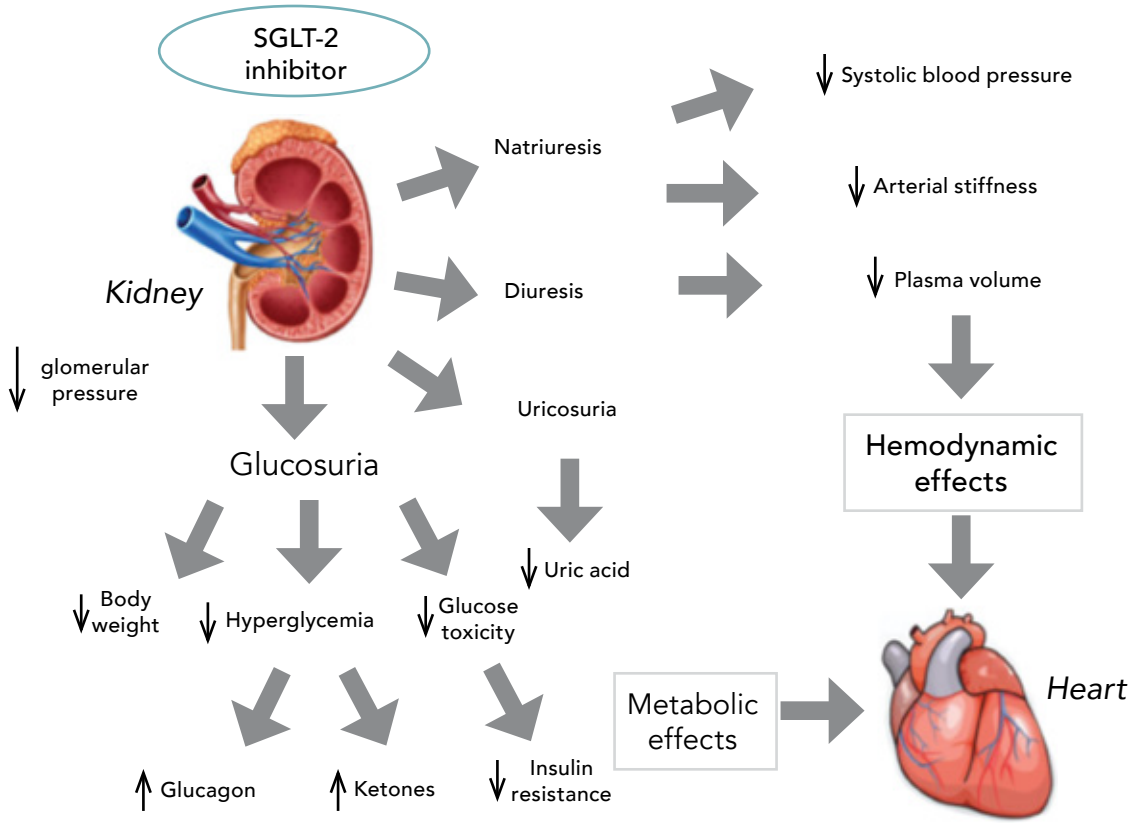
The American Diabetes Association (ADA) guidelines recommend a SGLT2i or a GLP-1 RA with demonstrated cardiovascular disease benefit as part of the glucose-lowering regimen for patients with T2DM who have established ASCVD or indicators of high risk, established kidney disease, or HF (Exhibit 4).[25] These are recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors. The European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) guidelines recommend the SGLT2i or GLP-1 RA before metformin if the patient is high risk.[26]

The SGLT2i do have some adverse events which should be considered. The main risk is genitourinary infections because of higher glucose in urine. Some of these can be severe and these agents should be avoided in those with chronic incontinence or who are unable to perform perineal hygiene. Euglycemic diabetic ketoacidosis can also occur. These agents should be withheld during significant illness, hospitalization, and for procedure/prep (colonoscopy). An increased risk of bone fracture was observed in the canagliflozin studies, and the package labeling contains a warning about the risk. Providers should consider factors that contribute to fracture risk before initiating canagliflozin.

Use of a SGLT2i is limited by kidney function. The package labeling for each agent has recommendations on kidney function levels where use is not recommended or contraindicated. Many guidelines support continued use of SGLT2i to eGFR ≥ 30 which contradicts the empagliflozin and dapagliflozin labeling. Canagliflozin has an indication to reduce the risk of ESRD, doubling of serum creatinine, CV death, and hospitalization for HF in adults with T2DM and diabetic nephropathy with albuminuria > 300 mg/day and has labeled dosing for eGFR of 30 and above.

Certain diabetes medications reduce CV events, including mortality, by 15 to 25 percent, but along with other mortality reducing classes they are not used frequently enough. In one analysis of claims data, guideline-directed therapy (high intensity statin, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker , and SGLT-2 inhibitor

Exhibit 3: Proposed Cardio-Renal Effects of SGLT2i[18]



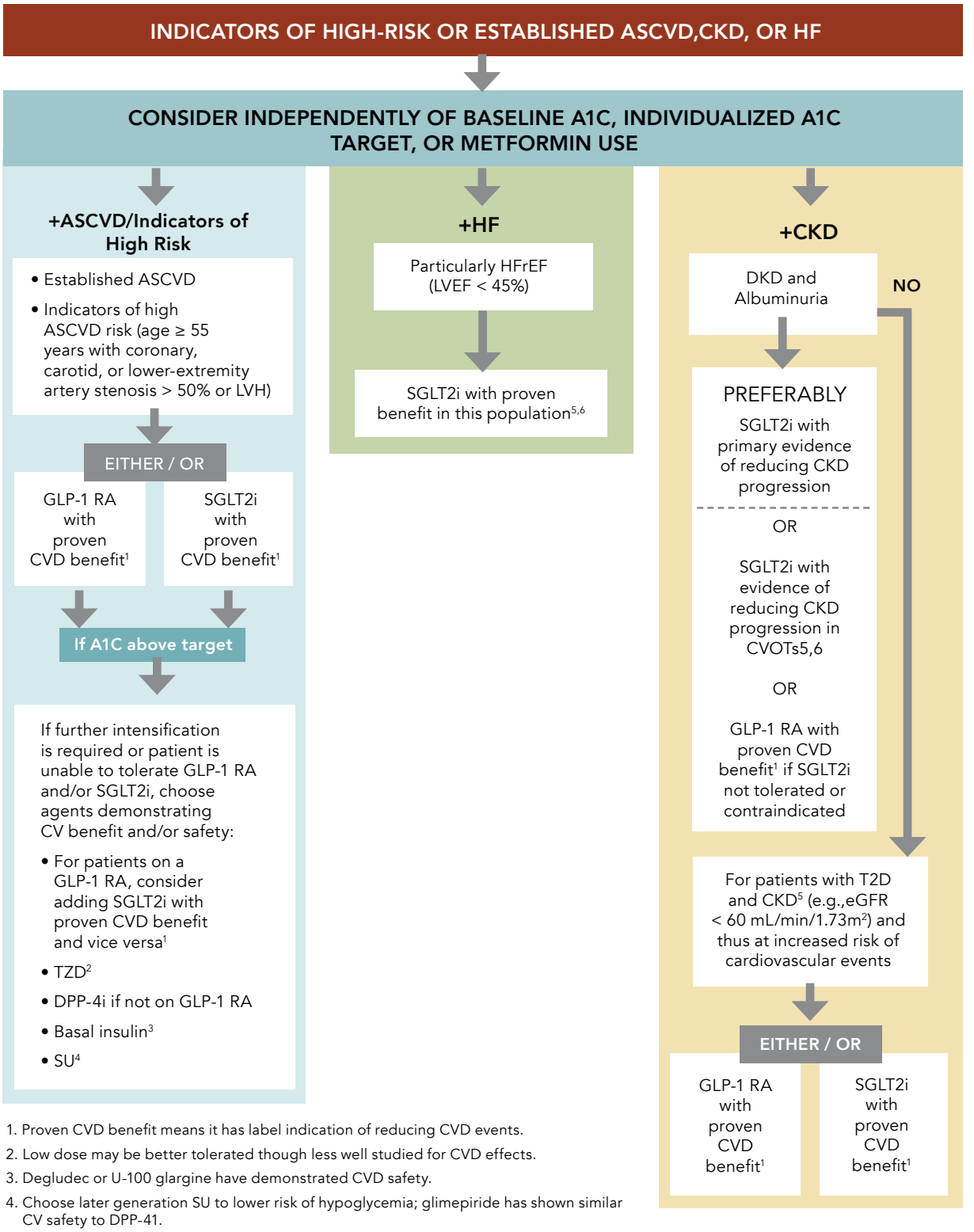
or GLP-1 RA) only occurred in 2.7 percent of patients.[27] Forty percent of patients were receiving at least one class, 19.4 percent two classes, and 37.4 percent no classes. Another analysis found that only 6.9 percent were receiving guideline-directed therapy.[28] In this analysis, SGLT2i and GLP-1 RA were used in 9.0 percent and 7.9 percent, respectively, whereas sulfonylureas were used in greater than 20 percent.

Barriers to the use of the guideline-directed diabetes medications include therapeutic inertia, lack of knowledge of benefits and risks of the newer agents, and concerns over real or perceived adverse events. Access and costs are also significant barriers. At least one SGLT2i and one GLP-1 RA are on formulary for most commercial and Medicaid plans. There is less consistency with Medicare plans. Other barriers include lack of coordination among those caring for patients with diabetes.

One way to improve care in those with T2DM is to revise traditional roles of various providers and have shared responsibility. The diabetologist has traditionally focused on blood glucose control and is the expert on the wide range of diabetes drugs, global care of diabetes, and microvascular complications. Often, they defer to the cardiologist for CV protection. The cardiologist traditionally has focused on management of cardiovascular disease and defers to the diabetologist or primary care provider on diabetes drugs. The primary care provider many times is trying to manage everything. There needs to be communication between each of a patient's providers to optimize care. COORDINATE-Diabetes is a randomized clinical trial to evaluate the effectiveness of implementing a clinic-level multifaceted intervention that includes establishing cardiology and diabetes care specialist partnerships, evidence-based care pathways, and measurement and feedback to improve the care of patients with T2DM and cardiovascular disease. Hopefully, when published, this study will provide some guidance on how to improve partnerships among care providers and increase the use of guideline-directed therapy.

Managed care can improve guideline-directed care that reduces risk of CVD and CKD by educating providers on appropriate use and eliminating barriers

Exhibit 4: ADA Choice of Diabetes Medication (After Metformin)[25]



1. Proven CVD benefit means it has label indication of reducing CVD events.
2. Low dose may be better tolerated though less well studied for CVD effects.
3. Degludec or U-100 glargine have demonstrated CVD safety.
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-41.
5. Be aware that SGL2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use.
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD in CVOTs. Canagliflozin, and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure data.

such as prior authorization and high copays for the SGLT2i and GLP-1 RA. They can also have a role in identifying those patients who are not receiving guideline-directed care for targeted interventions.

Conclusion

The SGLT2i and GLP-1 RA classes of diabetes medications have significant benefit beyond just glucose lowering; however, they are greatly under used. Given the high CVD and CKD rates in the T2DM patient population, improving use of guideline-recommended therapies, including SGLT2i and GLP-1 RA, is an important potential opportunity to improve care. This will in turn reduce the risk of recurrent ASCVD events, HF hospitalizations, and CVD mortality.

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Recent Advances in the Management of Epilepsy: Expert Treatment Strategies for Improving Clinical Outcomes

Joseph I. Sirven, MD

For a CME/CEU version of this article, please go to
http://www.namcp.org/home/education, and then click the activity title.

Summary

Treatment of epilepsy requires selecting a medication or combination which controls the patient's seizures without major adverse events, but no one regimen is ideal for all patients. In addition to selecting appropriate medications, adherence is important for achieving seizure control, and selecting tolerable agents is important for helping patients be adherent.

Key Points

- Seizures can be focal or generalized, and most are controlled with medication.
- Patients can and should be free of seizures without adverse events.
- The best antiepileptic medication for an individual depends on many factors.
- Medication adherence impacts seizure control.

A SEIZURE IS A SYMPTOM OF A DISTURBance in the brain and is caused by a sudden surge of abnormal electrical discharges from complex chemical changes in brain cells. It can be a manifestation or symptom of many medical problems. There are both provoked seizures and unprovoked seizures. Epilepsy is not a single entity or disease but is a family of syndromes. It is the tendency to have unprovoked recurring seizures not caused by any known medical condition. Diagnostically, epilepsy is defined as two or more unprovoked seizures greater than 24 hours apart, or one unprovoked seizure with risk of recurrent seizures or diagnosis of an epilepsy syndrome.[1] The term epilepsy is equivalent to seizure disorder, but seizures are not always due to epilepsy.

Exhibit 1 shows the three types of seizures. The diagnostic evaluation of a patient with a suspected seizure begins with a history including patient and observer descriptions of the seizure activity, medical history including medications, and family history. An electroencephalogram (EEG), brain MRI with epilepsy protocol, and laboratory testing to rule out reversible causes are all required for diagnosis.

Early diagnosis and appropriate medication are critical for reducing negative outcomes of epilepsy (Exhibit 2). For example, untreated focal seizures are often associated with poor school performance. Injury resulting from car accidents, burns, and falls also occur with uncontrolled seizures. Mortality occurs through injuries, drownings, and sudden unexpected death in epileptic persons (SUDEP). The risk of SUDEP in those with epilepsy is 1 per 1,000 person-years and in medically refractory epilepsy it is 1 per 500 person-years. The risk is higher in the setting of generalized tonic-clonic seizures (1 in 100). Epilepsy can also have a major social and professional impact on the patient.

Successful epilepsy treatment includes no seizures and no adverse events, prevention and treatment of comorbidities, and prevention of mortality. Clinicians and patients should not settle for any level of seizures or adverse events until all appropriate options have been explored.

The goal of no seizures may not be realistic for all people with epilepsy, and it is critical to explore shared realistic goals with the patient.

Exhibit 1: Types of Seizures

Focal (partial)	Generalized	Unknown Onset
• Onset within a network or group of neurons in one hemisphere or side of the brain. • May spread to affect networks on both sides, called bilateral (secondary generalized).	• Affects large networks throughout both sides of the brain.	Unclassified

The ideal antiseizure medication is broad spectrum (works against many seizure types), has no adverse events, is not teratogenic, does not affect bone health, weight, mood, behavior, or cognition, and is approved for all age groups. It should also be available in different formulations (tablets, liquids, sprinkles, intravenous), be accessible, and be affordable. Unfortunately, no ideal agent exists, but there are numerous effective options (Exhibit 3).

Antiepileptic medications are selected based on seizure type, medication characteristics, and patient characteristics. Some agents are only good for focal seizures and some for generalized. Medication characteristics to consider include metabolic route (kidney versus liver), dosing/formulation considerations, and adverse events including effects on bone health, weight, mood, behavior, and cognition. For example, levetiracetam, perampanel, and phenobarbital are more likely to have a negative impact on mood. A patient's comorbid conditions can also impact selection. For example, lamotrigine, valproate, and carbamazepine are good options when the patient also has bipolar disorder. Exhibit 4 shows other examples. Genetic mutations which lead to certain seizure syndromes can also impact treatment selection. Exhibit 5 shows some of the known mutations and their corresponding syndrome and treatment implications.[2-5]

Exhibit 2: Risks of Seizures—Why does it matter?

Exhibit 3: Antiepileptics by Class

Sodium+ Channel	Glutamate Receptors	GABA	SV_2A Receptor	Calcium Channel	Potassium Channel	Others
Phenytoin	Topiramate	Phenobarbital	Levetiracetam	Ethosuximide	Ezogabine	Cannabidiol
Carbamazepine	Zonisamide	Benzodiazepines	Brivaracetam			Everolimus
Oxcarbazepine	Perampanel	Tiagabine				Lamotrigine
Lamotrigine	Felbamate	Valproic acid				
Lacosamide		Vigabatrin				
Oxcarbazepine						
Rufinamide						
Eslicarbazepine						
Cenobamate						

SV_2A = synaptic vesicle protein

For many patients, a combination of two or more antiepileptic medications will be needed to adequately control seizures. In this case, agents should be selected from different classes. Medical marijuana for epilepsy has been a hot topic in recent years. The active compound in epilepsy is likely cannabidiol (CBD). In a double-blind, placebo-controlled trial in 120 children with medication resistant Dravet syndrome, CBD oil reduced seizure frequency by 22.8 percent compared to placebo.[6] Importantly, the rate of adverse events was much higher with CBD oil compared to placebo (75% versus 38%). A proprietary oral solution of highly purified plant-derived CBD oil (Epidiolex®) is FDA-approved for treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients one year of age and older. Although not FDA-approved, the highly purified CBD oil may be an option for treatment-resistant epilepsy.

There are several issues with using CDB for seizure treatment. Drug interactions between CBD and other antiepileptic medications are not well studied. CBD may increase serum levels of clobazam and, in particular, the active metabolite of clobazam (N-desmethylclobazam).[7] It is important that only the FDA-approved product be prescribed because CBD oil available from other sources, such as medical marijuana dispensaries, is not standardized and an FDA audit found minimal or no CBD content in many marketed products.[8,9] There are also legal issues with using any CBD product other than the FDA-approved product.

Exhibit 4: Selection of Antiepileptic Medication Based on Comorbid Conditions

- Bipolar Disorder
  - Lamotrigine, valproate, carbamazepine
- Migraine
  - Topiramate, gabapentin, valproate
- Neuropathy/Neuropathic Pain
  - Gabapentin, pregabalin
- Trigeminal Neuralgia
  - Carbamazepine, oxcarbazepine, gabapentin
- Tremor
  - Phenobarbital, gabapentin

Everolimus (Afinitor®), a mammalian target of rapamycin (mTOR) inhibitor FDA-approved for treating several types of cancer, was being used to treat benign tumors associated with tuberous sclerosis complex when it was found to reduce seizure frequency in these patients. In a Phase III, randomized, double-blind, placebo-controlled study in 366 patients with tuberous sclerosis complex and treatment-resistant seizures (≥16 in an 8-week baseline phase), adjunctive everolimus treatment

Exhibit 5: Potential Impact of Genetics on Treatment[2-5]

Mutation	Syndrome	Treatment Decision
SCN1A	Dravet syndrome	Avoid phenytoin and lamotrigine (generally but not always)[b]
SCN2A	Benign familial neonatal-infantile seizures	High-dose phenytoin helpful
SCN8A	Epilepsy with encephalopathy	High-dose phenytoin helpful
SLC2A1	GLUT1 encephalopathy, early-onset childhood absence epilepsy, and paroxysmal exertional dyskinesia.	Ketogenic diet
PRRT2	Benign familial infantile seizures, and infantile convulsions and choreoathetosis	Carbamazepine
PLCB1	Severe epileptic encephalopathy	Inositol
ALDH7A1	Pyridoxine-dependent epilepsy	Pyridoxine
PNPO	Pyridoxal 5′-phosphate-dependent epilepsy	Pyridoxal-5′-phosphate
KCNQ2	Benign familial neonatal seizures	Consider ezogabine for loss-of-function variants
KCNT1	Malignant migrating focal seizures of infancy; autosomal dominant nocturnal frontal lobe epilepsy	Consider quinidine for gain-of-function variants[a]
GRIN2A	Landau-Kleffner syndrome, epilepsy-aphasia spectrum disorders	Consider memantine, dextromethorphan for gain-of-function variants[a]
TSC1	Focal cortical dysplasia, tuberous sclerosis complex	Consider everolimus
TSC2	Severe recurrent seizures; tuberous sclerosis complex	Consider everolimus or other mTOR inhibitors[a]
CLN2	Batten disease	Cerliponase alfa

[a] Trials needed
[b] In late infancy and childhood
mTOR = mammalian target of rapamycin

significantly reduced seizure frequency with a tolerable safety profile compared with placebo.[10] The recommended dose is 5 mg/m^2 orally once daily. Stomatitis, pneumonia, irregular menstruation, hypercholesterolemia, and neutropenia are potential adverse events. Everolimus increases pre-dose concentrations of the carbamazepine, clobazam, oxcarbazepine, and clobazam's metabolite N-desmethylclobazam by about 10 percent.

Seizure rescue medication prescriptions may be necessary for some patients. Rescue medications are important because it is more difficult to stop a prolonged seizure than a brief seizure, and longer seizures lead to long recovery periods. Rescue medication prevents progression to status epilepticus, unnecessary transport to emergency rooms, and the cost of escalated care. Availability of rescue medication is especially important in areas where emergency medicine services take a long time to respond (such as rural areas) or are overburdened. Midazolam (intranasal), lorazepam (oral solution), diazepam (oral solution, intranasal, rectal), and clonazepam (oral disintegrating tablets) are all used as rescue medications. Significant patient and caregiver education is required on the appropriate times to administer and to provide administration instructions for rescue medications. Adverse events can include decreased respirations, oversedation, and cardiopulmonary instability. These events can vary in severity depending on the dose of seizure rescue medication, duration of the seizure, and interaction with other medications. Because of potential adverse

events, someone trained in cardiopulmonary resuscitation should be available to the patient if seizure rescue medication is prescribed.

Nonadherence is a common problem among patients with epilepsy and can significantly impact its successful treatment. One retrospective claims assessment found that 39 percent of adults with epilepsy were nonadherent and another study found that less than 50 percent of patients remained adherent at 12 months following medication initiation.[11,12] Nonadherence is associated with increased risk for seizure. In a retrospective claims analysis, after controlling for covariates, the risk for seizure was 21 percent higher for nonadherent patients compared with adherent patients ($p = 0.0002$).[12]

In addition to patient education on the importance of medication adherence and adherence monitoring, providers can select therapies which require fewer daily doses to help facilitate adherence. Multiple once-daily options are available and include eslicarbazepine, phenytoin, phenobarbital, zonisamide, perampanel, and various extended-release formulations. Valproate, lamotrigine, levetiracetam, oxcarbazepine, topiramate, and gabapentin are all available as extended-release once-daily formulations. Theoretically, the extended-release formulations should have less impact of dose-related adverse events due to more steady blood levels.

Seizures do not respond to medical treatment in 30 to 40 percent of people.[13,14] People with epilepsy syndromes are more likely to have persistent, harder to treat seizures. Approximately 47 percent of people with new onset epilepsy respond to the first agent used, and 14 percent respond to a second or third agent.[14] For those who do not respond to optimized medications, surgery and implanted devices may be an option.

Epilepsy surgery can be curative for temporal lobe and extratemporal seizures where a focal site in the brain can be removed. Implanted devices, such as deep brain stimulators and vagal nerve stimulators, can be palliative for other types of epilepsy. Although an option for debilitating seizures despite optimal medical treatment, many appropriate patients are not offered these options.

Conclusion

Early diagnosis and treatment of epilepsy is critical towards improving outcomes and reducing mortality. The risk of adverse events compared to the benefits of seizure control must be considered when selecting therapy. About 60 percent of patients with epilepsy will respond to antiepileptic medication therapy. For those with medication resistance, surgical options offer the potential for cure or palliation.

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New Treatment Breakthroughs in the Management of HIV: Expert Strategies for Optimized Clinical and Economic Outcomes

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For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

There are more than a million people in the United States (U.S.) living with HIV, and over 30,000 new cases are added each year. Despite the availability of effective therapy, many patients do not achieve viral suppression which prevents transmission to others. Several new antiretrovirals have been approved in recent years that target nonadherence and drug resistance.

Key Points

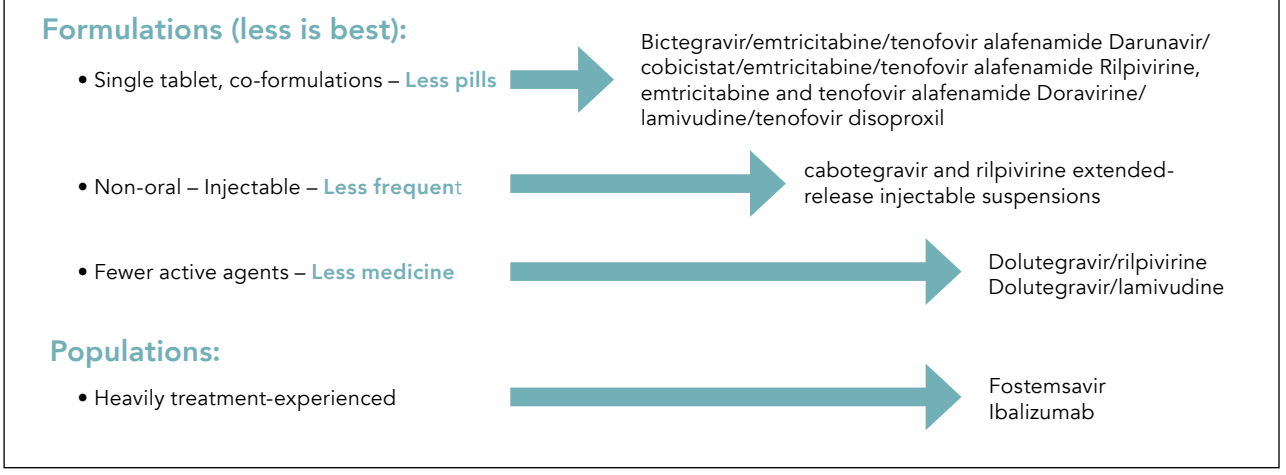
- Two one tablet per day complete regimens are now available.
- A long-acting combination of two injections has been approved.
- Two therapies with new mechanisms of action are available for heavily treatment-experienced patients with an abundance of drug resistance.

FOR 2018, THE CENTERS FOR DISEASE Control and Prevention (CDC) estimated that 1,173,900 persons 13 years of age and older were living with human immunodeficiency virus (HIV) infection in the U.S. (includes an estimated 161,800 undiagnosed persons).[1] Annual infections in the U.S. have been reduced by more than two-thirds since the height of the epidemic in the mid-1980s, but progress stalled during 2014 through 2018. An estimated 36,400 new HIV infections occurred in the U.S. in 2018. HIV continues to have a disproportionate impact on certain populations, particularly racial and ethnic minorities, and gay and bisexual men.[2] Deaths from HIV have been significantly reduced, and there is no longer a gap in life expectancy for those infected; however, there is still a significant gap for comorbidity-free life expectancy in people living with HIV (PLWH) compared to non-infected controls (13 to 14 years versus 29 years).[3]

The economic impact of HIV infection is complicated and dependent on multiple factors. This includes clinical stage at the time of diagnosis, opportunistic infections, geography, health insurance status, demographics (race, ethnicity), comorbidities, and others. HIV infection definitely has an impact on employment, earnings, housing, savings, and net worth. The lifetime cost to treat one person living with HIV has been estimated to be $485,000. Antiretroviral therapies (ART) are the primary driver of costs for HIV care. Other factors include screening, health care visits, laboratory testing, and hospitalization.

The U.S. has the highest ART costs yet the lowest rate of HIV viral suppression (54%) compared with all other well-resourced countries, including Britain, Australia, and Canada.[4] Costs of recommended regimens have been rising. The average annual cost of recommended ART has increased 34 percent since 2012, 3.5 times faster than inflation.[5] Although prevalence of HIV is low in the U.S., ART is the nation's fifth costliest therapeutic class, accounting for $22.5 billion in spending in 2018. The federal "Ending the HIV Epidemic" initiative aims to achieve a 90 percent decrease in new HIV infections by 2030. To do so, the U.S. needs to increase viral suppression by 33 percent, which will require a total

Exhibit 1: What's New in ART?



of $35.6 billion in annual spending on ART alone.

The U.S. Department of Health and Human Services provides continually updated guidelines for managing HIV.[6] Clinicians must consult the guidelines for the most up to date recommendations for starting and modifying therapy.

Managing the antiretroviral (ARV) category of therapy can be a challenge for managed care because there are more than 30 agents in seven classes FDA-approved for treatment of HIV infection. The classes include the nucleoside/nucleotide reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), integrase strand transfer inhibitor (INSTI), fusion inhibitor, C-C chemokine receptor type 5 (CCR5) antagonist, and CD4 T lymphocyte post-attachment inhibitor. In addition, two drugs, ritonavir and cobicistat are used as pharmacokinetic (PK) enhancers (or boosters) to improve the PK profiles of PIs and the INSTI elvitegravir. ART for a treatment-naïve patient generally consists of a three-drug regimen – two NRTI in combination with one of three drug classes. INSTI, NNRTI, or PI with a booster (cobicistat or ritonavir)] or a two-drug regimen (INSTI plus NRTI).

Several new agents or formulations have been marketed which can improve care through improved formulations or targeting difficult to treat populations (Exhibit 1). Combinations of two or three medications in a single formulation allows a one tablet a day regimen, which significantly reduces the tablet burden for patients. Two examples which are included in the guideline recommendations for initial regimens for treatment naïve patients are bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®) and dolutegravir/lamivudine (Dovato®). Other advancements have been options for heavily treatment-experienced (HTE) patients, ibalizumab-uiyk (Trogarzo®) and fostemsavir (Rukobia®), which have new mechanisms of action. Most recently, the first long-acting injectable was approved [cabotegravir and rilpivirine extended-release injectable suspensions (Cabenuva®)]. In determining where these newer agents fit in the overall treatment scheme, efficacy, tolerability, resistance development, and guideline recommendations are all important.

Bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) is a fixed-dose, once-daily combination tablet containing a novel INSTI and two NNRTI. This combination is indicated as a complete regimen in HIV-1 infected adults with no history of ART or to replace the current ART regimen of patients who are virologically suppressed on a stable ARV regimen for at least three months and no history of treatment failure or resistance to its individual components.[7] In the trials comparing it to already approved combinations, the primary endpoint of viral load < 50 copies/mL was achieved in 92 percent of the BIC/FTC/TAF group and 93 percent of the abacavir/lamivudine/dolutegravir group and in 89 percent of the BIC/FTC/TAF group and 93 percent of the dolutegravir plus emtricitabine/tenofovir alafenamide group.[8,9] Another trial tested the efficacy and safety of BIC/FTC/TAF in virologically suppressed patients

Exhibit 2: Factors in Selecting ART

Patient
• Gender (tolerability differences)
• Co-morbid conditions (renal function, CVD risk, obesity, low BMD, HBV)
• Pregnancy plans (especially for INSTI)
• Drug resistance
• Age?
• Adherence barriers (single tablet daily or injectable may be option)
Medication
• Drug interactions (especially for cobicistat and ritonavir)
• Tablet burden
• Adverse events (kidney, lipids, bones, weight gain)

CVD = cardiovascular disease; BMD = bone mineral density, HBV = hepatitis B

switched from their current ART regimens, and no differences in virologic control was found (94% versus 95%).[10]

Combination dolutegravir/lamivudine (DTG/3TC), approved in 2019, was the first two-drug, fixed-dose complete regimen for the treatment of HIV-1 infection in treatment-naïve adult patients. This contrasts with the traditionally required three-drug standard-of-care regimen options. This combination offers a new opportunity in patients who cannot tolerate any of the more common three-drug regimens due to adverse events or unavoidable drug interactions. The efficacy and safety of combination DTG/3TC were demonstrated in two identical studies, GEMINI-1, and GEMINI-2. A total of 1,433 HIV-1-infected, treatment-naïve adults were randomized to receive a two-drug regimen, dolutegravir 50 mg plus lamivudine 150 mg, or a three-drug regimen, dolutegravir plus emtricitabine plus tenofovir disoproxil fumarate. The primary endpoint of achieving a viral load < 50 copies/mL showed DTG/3TC to be noninferior (91% of the 716 two-drug patients versus 93% of the 717 three-drug patients) when the results of the two studies were pooled together.[11] Fewer patients had drug-related adverse events in the two-drug regimen as opposed to the three-drug regimen (18% and 24%, respectively). Renal and bone adverse events were significantly lower with DTG/3TC, whereas non-HDL lipid changes were significantly lower with the three-drug regimen. No treatment-emergent resistance was observed in any of the study patients. Due to noninferior efficacy and a similar tolerability profile, this fixed-dose combination of DTG/3TC was included in the treatment guidelines as a recommended initial regimen for most PLWH.[6] This combination has also been studied as a switch regimen in those who are virologically suppressed and is approved for this indication.[12,13]

A newly approved (January 2021) two-medication regimen of long-acting injectable cabotegravir, INSTI, and long-acting injectable rilpivirine, NNRTI (Cabenuva®) is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.[14] Prior to initiating the injectable, oral lead-in dosing with the separate components should be used for approximately one month to assess the tolerability to each component. Injectable therapy is initiated on the last day of oral dosing with monthly intramuscular injections (each medication requires a separate intramuscular injection). Higher doses (cabotegravir 600 mg and rilpivirine 900 mg) are used for the first injection; subsequent injections are 400 mg and 600 mg.

Trials have examined use of this combination as switch therapy and for treatment naïve patients. Monthly injections were noninferior to standard oral therapy for maintaining HIV-1 suppression.[15] In treatment naïve patients, viral suppression at week 48 was found in 93.6 percent who received long-acting therapy and in 93.3 percent who received oral therapy.[16] Overall, six patients developed resistance despite good adherence and decent drug levels in the combination injection therapy trials.[17] Five of six had the A1 HIV subtype. All but one case had the L74I INSTI resistance mutation at baseline. This mutation is more common in Russia than in the U.S.

Overall, these newer regimens are generally as efficacious as predecessors. The injectable regimen may be less well tolerated than the older and newer oral regimens, but some patients may prefer the injectable for intermittent dosing versus daily therapy. Some newer regimens have lower barrier to resistance but emergent resistance is uncommon in the U.S.

A small percentage of PLWH in the U.S. are HTE but for those patients two new agents may be helpful. Ibalizumab-uiyk is a recombinant monoclonal antibody given by infusion that binds to the surface proteins of CD4 cells, leading to conformational

Exhibit 3: Considerations When Switching Regimens in Virologically Suppressed Patients[6]

Drug Resistance:

- Review ART history for possible viral failure.
- Review all available resistance test results.
- If earlier resistance uncertain, only consider switch if new regimen likely to maintain suppression of resistant virus.
- Caution when switching from boosted PI to another class if full treatment/resistance history not known.
- Consult an expert when switching if resistance to ≥ 1 class.
- Within-class switches usually maintain virologic suppression if no resistance to drugs in that class are present.

Safety:

- Review ART history for intolerance.
- Must be HLA-B*5701 negative if considering abacavir.
- Consider drug–drug interactions with comedications.

Comorbidity:

- Hepatitis B coinfection.
- Cardiovascular disease or risk.
- Renal function.
- Bone mineral density.
- Pregnancy.
- Other coinfections.

changes that prevent the steps required for HIV-1 fusion and entry into the cell. Because of its unique binding specificity, ibalizumab blocks viral entry without causing immunosuppression. It is indicated in combination with other ARV for treatment in HTE adults with multidrug-resistant (MDR) HIV-1 who are failing their current ARV therapy regimen and was FDA-approved in 2018.[18] Approval of ibalizumab was based on a trial conducted on 40 HTE HIV patients with viral load greater than 1,000 copies/mL and a documented resistance to at least one NRTI, NNRTI, and a protease inhibitor. At the end of 25 weeks, 43 percent of patients achieved a < 50 copies/mL viral load.[19] The most common adverse events associated with ibalizumab were nausea, dizziness, and diarrhea. Careful monitoring is required for one hour after administration of the first infusion for infusion-related reactions. Because this is an infusion, there are logistical issues for HIV treatment providers to overcome in accessing this treatment for appropriate patients.

Fostemsavir is the first FDA-approved attachment inhibitor and is indicated for combination therapy in HTE adults with known MDR HIV-1, specifically for patients who are failing current ART due to potential resistance, intolerance, or safety considerations.[20] Binding of this agent to gp120, a viral envelope glycoprotein necessary for viral attachment to CD4 cells, prevents viral entry into CD4 cells, effectively stopping viral replication. Fostemsavir was evaluated for both safety and efficacy in a randomized, double-blind, placebo-controlled clinical trial (BRIGHTE) with 371 HTE HIV-1 subjects. This study had two cohorts – a randomized cohort, in which patients with one or two fully active ARVs remaining received oral fostemsavir (600 mg twice a day) or a placebo in combination with their failing regimen for eight days, followed by fostemsavir plus optimized background therapy; or the non-randomized cohort, in which patients with no remaining antiretroviral options received oral fostemsavir (600 mg twice a day) plus optimized background therapy from the start. In the randomized cohort, rates of virological suppression (HIV-1 RNA < 40 copies/mL) increased from 53 percent at week 24 to 60 percent at week 96.[21] Response rates in the non-randomized cohort were 37 percent at week 24 and week 96. Mean CD4 counts increased from baseline at week 96. Mean CD4/CD8 ratio increased from 0.20 at baseline to 0.44 at week 96 in the randomized cohort. Few adverse events led to discontinuation (7%). The most commonly reported adverse event from fostemsavir was nausea. More severe reactions, including elevations in liver enzymes, were reported in patients with hepatitis B or C coinfection.

Most ART works well in most people, but Exhibit 2 shows some of the factors that should be considered in selecting both first-line therapy and in case of virologic failure. Weight gain can be substantial for some of the medications. While some of this weight gain may be an appropriate return-to-health effect, excessive increases in weight may lead to obesity and increases cardiovascular disease, diabetes, and

cancer risk.[22] Factors associated with weight gain include lower CD4 cell count, higher HIV type 1 RNA, no injection drug use, female gender, and African American race. INSTI use is associated with more weight gain than PI or NNRTI, with dolutegravir and bictegravir associated with more weight gain than elvitegravir/cobicistat. Among the NNRTI, rilpivirine was associated with more weight gain than efavirenz. Tenofovir alafenamide was associated with more weight gain than tenofovir disoproxil fumarate, abacavir, or zidovudine.

Considerations when switching regimens in virologically suppressed patients are shown in Exhibit 3.[6] The guidelines provide recommendations on regimens to switch to for patients who are virologically suppressed or have virologic failure

The newer ART that have been discussed here are expensive, but they may provide value for managed care because of advantages of better adherence and tolerance. Policies for identifying appropriate patients for the long-acting injectable combination and the two therapies for HTE patients will need to be established to manage use of these agents.

Conclusion

HIV has become a manageable chronic disease, but there are definitely areas where care can be improved, especially viral suppression rates. Advances in antiretroviral therapy in the last few years have been significant. Now there are one tablet a day regimens and monthly injections which will hopefully improve adherence and viral suppression.

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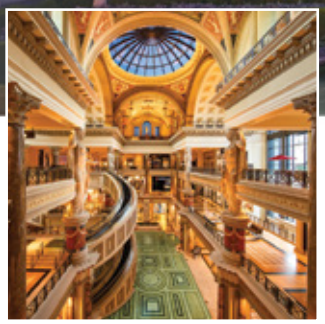

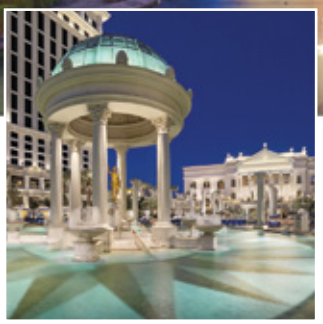

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