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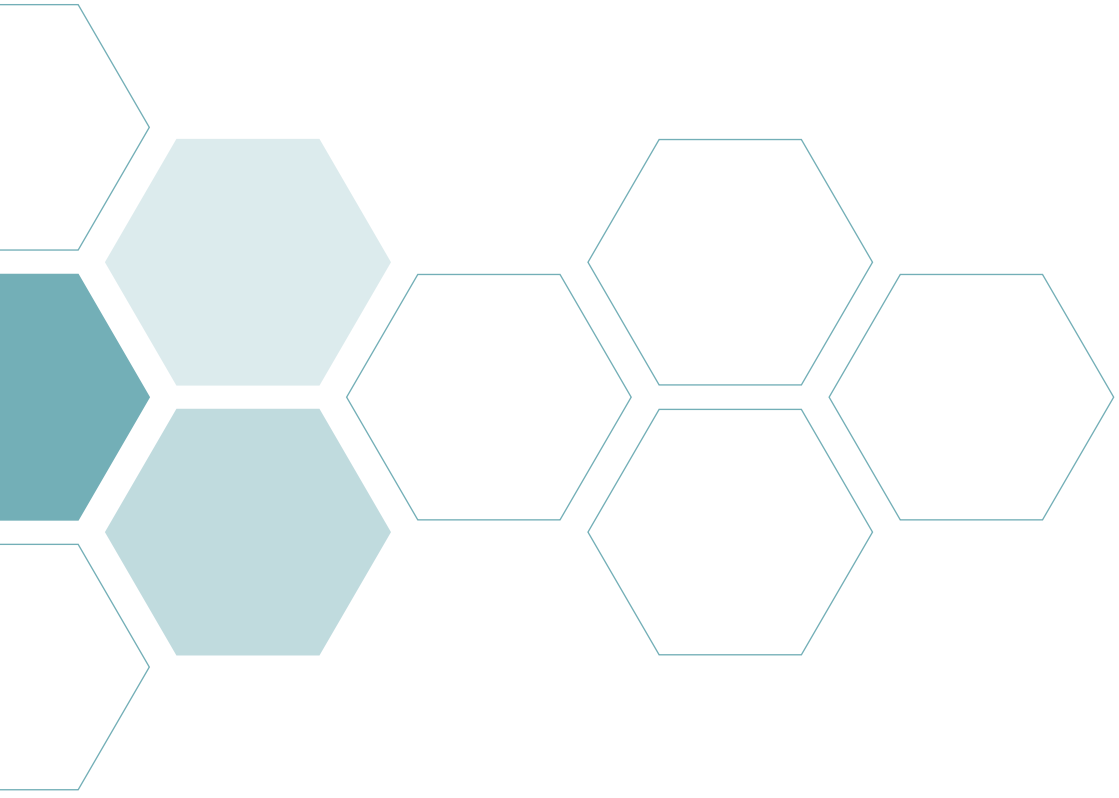

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TABLE OF CONTENTS

Editorial Review Board

Expanding the Treatment Armamentarium for Amyotrophic Lateral Sclerosis (ALS): What Managed Care Needs to Know

Hiroshi Mitsumoto, MD, DSc

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

Summary

Amyotrophic lateral sclerosis (ALS) is a devastating neurogenerative disease that is complex and costly to manage. Significant improvements in care have been made in the past 20 years which are improving survival, but it is still a fatal disease. A better understanding of the pathophysiology and genetic basis of the disease is needed to find a cure.

Key Points

- ALS is a rare and fatal syndrome with an unknown cause.
- The disease process begins many years before symptoms appear.
- Disease-modifying therapies (DMTs), nutritional interventions, respiratory care interventions, and aggressive symptomatic management are key to improving quality of life and prolonging survival.
- Multi-disciplinary care is also important for achieving both outcomes.

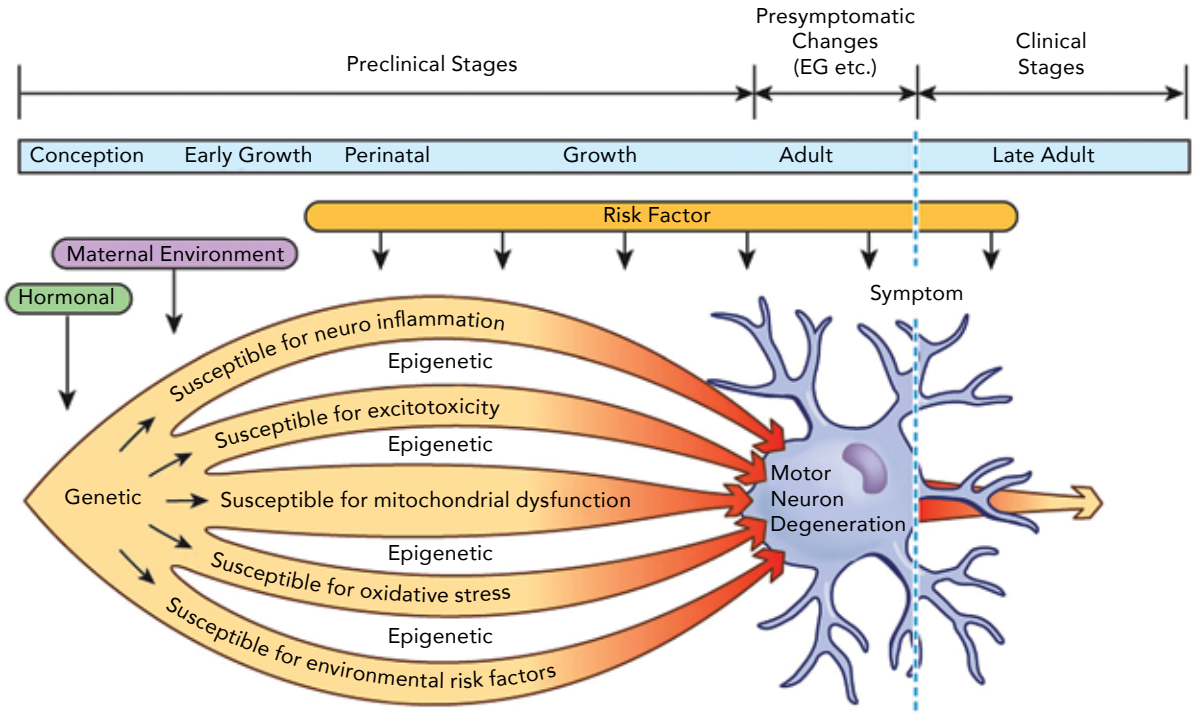
AMYOTROPHIC LATERAL SCLEROSIS (ALS) is a rare progressive neurodegenerative disorder affecting upper and lower motor neurons and is more commonly known as Lou Gehrig's disease. ALS and other neurodegenerative disorders are similar in that they affect similar patient populations and have an unknown cause and no cure. With ALS, there is a highly predictable prognosis in half of patients and unique loss of function. ALS leads to the inability to move, speak, eat, and eventually breathe. Some neurologic functions, including cognition, extraocular movements, bowel and bladder function, and sensation, are typically not affected in ALS patients. At least half of patients with classical ALS have subtle frontal and temporal lobe impairment or mild cognitive impairment, including problems with memory or decision-making. Approximately 5 percent of patients develop frontotemporal dementia (FTD).

In the United States (U.S.), the prevalence of ALS is 5.2 in 100,000 individuals, with an incidence of 1.7 per 100,000 people, reflecting short average survival.[1-3] It is estimated that 30,000 individuals in the U.S. have ALS. The five-year survival rate is 25 percent and 10-year survival is approximately 10 percent. In the U.S., Caucasians have a higher rate than other groups and men have a higher rate than women (3 to 2 ratio).[3]

Genetic factors cause 5 to 10 percent of cases, known as familial ALS (fALS), and 90 to 95 percent of cases are considered sporadic (sALS).[1] More than 30 ALS-specific genetic mutations have been identified to date. The most common is the C9orf72 mutated gene, which accounts for approximately 30 to 40 percent of all fALS cases. Superoxide dismutase one (SOD1) mutations account for about 20 percent of fALS cases. Many of the same gene mutations have been identified in seemingly sporadic patients.

At the beginning, ALS may involve degeneration and death of only upper motor neurons (UMN) or lower motor neurons (LMN), but it eventually progresses to involve both. Similar to many other degenerative diseases, there is a long preclinical process with ALS (Exhibit 1).[4] Motor neurons are

Exhibit 1: ALS Begins Much Earlier Than Symptom Onset[4]



markedly depleted when weakness is detected and even when muscle strength is normal.[5] There can be more than 30 to 50 percent neuronal loss and normal strength. When weakness is detected, 80 percent of neurons can be depleted. As early as postnatal seven days, morphological changes of motor neurons are detected in SOD1 mutated mice.

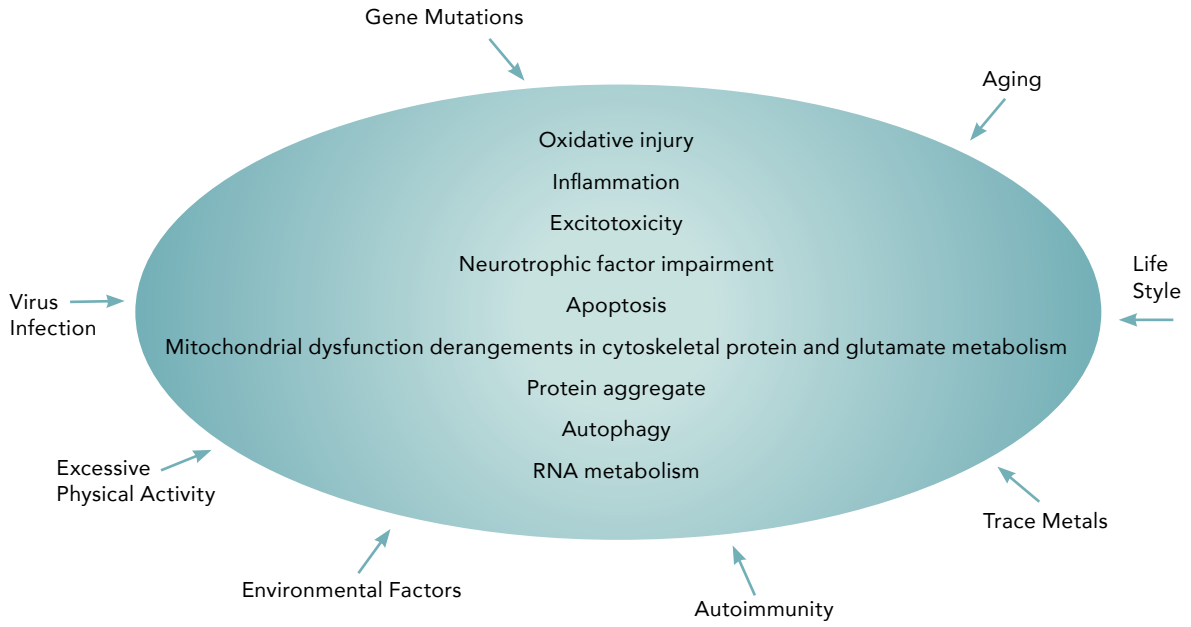
Most experts consider ALS a syndrome because there are many different presentations (clinical heterogeneity). As noted previously, there are familial and sporadic cases. There are also different types of onset including spinal (classical ALS), bulbar (speech and swallowing), and respiratory. There are also variants, including unilateral (Mills' variant) and mononeuritis/monomeric. Disease progression is vastly different among patients, with some having very rapid progression and others having a much slower disease process. It is likely that various genes are involved, which leads to the different presentations.

It is unknown what exactly starts the process of UMN and LMN loss. Most investigators and clinicians agree that various factors, including oxidative injury linked to free radical formation, inflammation, excitotoxicity, neurotrophic factor impairment, apoptosis, mitochondrial dysfunction, protein aggregates, autophagy, derangements in cytoskeletal protein and glutamate metabolism, defects in axonal transport, and RNA metabolism, are involved in the pathogenic process of ALS (Exhibit 2). It appears that the process is triggered in a genetically susceptible person who encounters risk factors such as excessive physical activity or environmental exposure.

The diagnosis of ALS is made possible by history, physical and appropriate neurological examinations; electrophysiological examinations; neuroimaging (to rule out multiple sclerosis, brainstem strokes, tumors, spinal radiculopathy, and others); clinical laboratory testing; neuropathologic examinations, and repetition of clinical and electrophysiological examinations at least six months apart to ascertain evidence of progression.[6,7] Signs of LMN degeneration by clinical, electrophysiological or neuropathologic examination and signs of UMN degeneration by clinical examination are required. Motor neurons from three or four of the following regions have to be involved: bulbar (jaw, face, palate, larynx, and tongue), cervical (neck, arm, hand, and diaphragm), thoracic (back and abdomen), and lumbosacral (back, abdomen, leg and foot).

Unfortunately, it typically takes a long time to diagnose ALS. Studies and patient databases have shown that it takes an average of 10 months from

Exhibit 2: Pathogeneses of Motor Neuron Death in ALS



symptom onset.[8] There are many reasons for the delay, including initial ill-defined and nonspecific symptoms, awaiting disease progression to meet diagnostic criteria, no diagnostic biomarkers, doctors treating the symptoms as other diseases (e.g., carpel tunnel syndrome), and prolonged waits for an ALS specialist's second opinion.

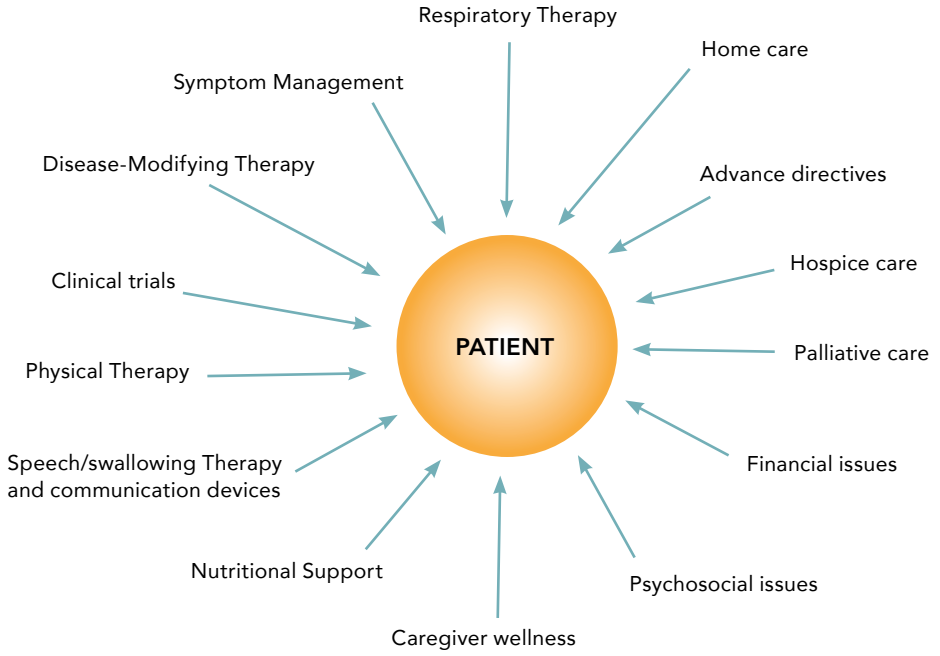
ALS has a major impact on patients and caregivers. The receipt of a "death sentence" diagnosis is devastating, leading to tremendous emotional distress and anxiety. Patients have difficulty transitioning from being the main financial supporter of the family to becoming a dependent family member. The pace of disease progression can outpace learning and coping. For example, the patient starts out with a foot drop and learns to use a brace to manage. Just when they have mastered the brace, they have progressed and need a walker and then rapidly progress to need a wheelchair. Families and caregivers have high physical and psychological burdens, anxiety, depression, distress, and low quality of life (QOL). Eventually, the home becomes a "mini-hospital."

Good ALS patient care requires clinicians to have a firm understanding of the disease and its treatment, along with an interest and commitment to bettering the lives of those affected. There is greater hope for treating this disease now, and clinicians must convey this important message to patients and their families.

The American Academy of Neurology (AAN) has published practice parameters for managing the various aspects of the disease.[9,10] Care of the patient with ALS is complex and requires aggressive symptomatic treatment, disease-modifying therapies (DMTs), nutritional care, pain and discomfort relief, assistive devices (breathing, ambulation, communication), and terminal and palliative care (Exhibit 3).

Because the care of patients with ALS is complex, it is best accomplished in a multidisciplinary clinic, which has been shown to prolong survival by eight to 10 months and improve QOL.[10] Additional advantages of multidisciplinary care include more and effective symptomatic treatment and sensitive discussions regarding the diagnosis with patients, virtual problem solving by multiple experts, minimized patient travel time visiting different professionals or therapists, highly specialized health care professionals, and how clinical research and trials can be effectively performed. There are more than 100 ALS Centers in the U.S., but some areas of the country lack these facilities. The major disadvantages of multidisciplinary care are high costs and the tiring of both patients and providers. The AAN practice parameters recommend patients with ALS should be considered for referral to a specialized multidisciplinary ALS clinic to optimize health care delivery (Level B), prolong survival (Level B), and

Exhibit 3: Managing the ALS Patient



enhance quality of life (Level C).[10]

Symptomatic management is important in maintaining QOL. Clinicians need to identify symptoms that bother the patient and aggressively manage those. These can be psychological, musculoskeletal (cramps), gastrointestinal, pulmonary, emotional (pseudobulbar affect), and others (fatigue, insomnia, drooling, etc.). The easiest and safest symptomatic medications should be tried first before those with potentially more adverse events and those more difficult to manage.

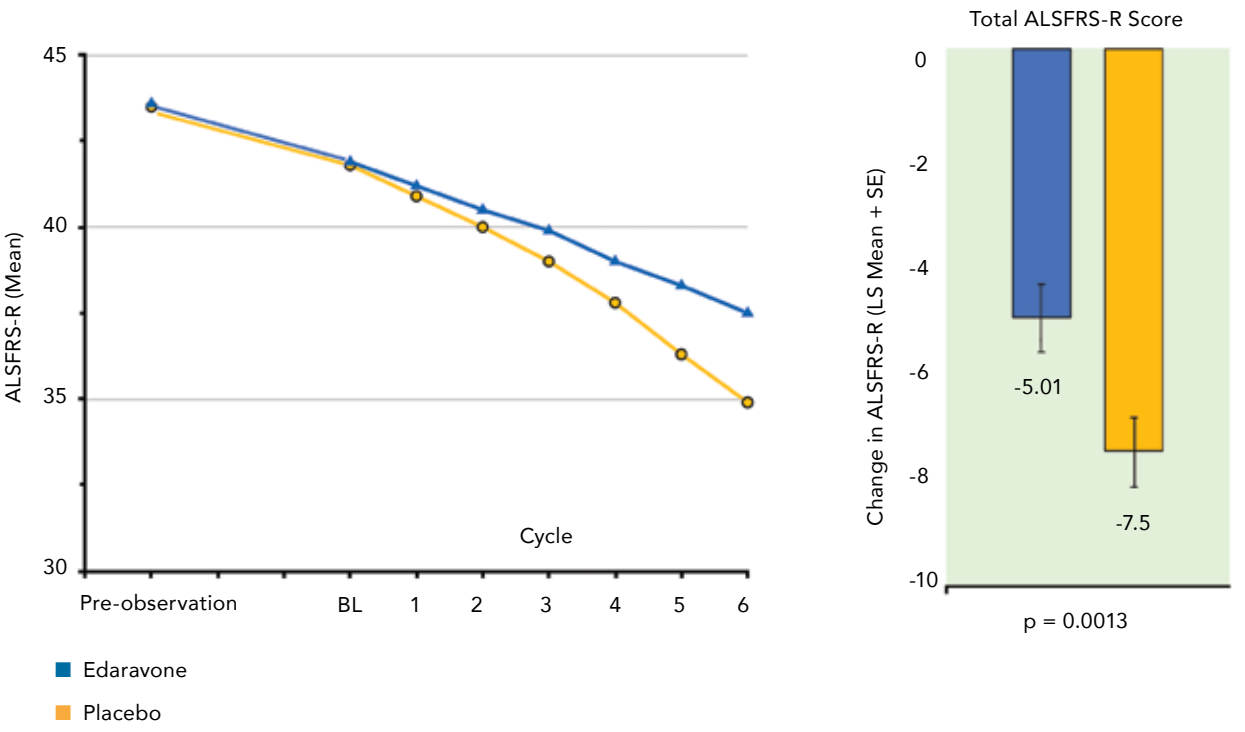
Two important interventions in ALS are percutaneous endoscopic gastrostomy (PEG) tubes for maintaining nutrition and noninvasive ventilation (NIV). In patients with ALS with impaired oral food intake, enteral nutrition via PEG should be considered to stabilize body weight and for prolonging survival.[9] To optimize safety of the procedure, PEG placement for dysphagia in ALS may be considered when forced vital capacity (FVC) is close to 50 percent of predicted. FVC is the most used measure of respiratory muscle function for prediction of survival and disease progression. FVC less than 50 percent predicted increases the risk of anesthesia. NIV should be considered to treat respiratory insufficiency in ALS, both to lengthen survival and probably to slow the rate of FVC decline.[9] 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 this type of ventilation.

There are now two agents approved for treating ALS. Expectations about therapeutic medications from clinicians and patients are somewhat different (Exhibit 4). There are many reasons why it difficult to

Exhibit 4: Expectations of Therapeutic Medications

TREATING CLINICIANS
• Visible difference in all patients or at least some patients
• Significant "statistical significance" by simple analyses
• Balance among effect, toxicity, and cost
• Hope
PATIENTS
• Cure
• Visible differences
• Low cost
• Hope

Exhibit 5: 33% Less Functional Loss with Edaravone Compared to Placebo over a 24-week Double-Blind Period[18]



BL = baseline; ALSFRS-R = ALS Functional Rating Scale – Revised

find effective medications for ALS. ALS is a syndrome consisting of many different conditions or expressions which may have multiple etiologies. Biological onset occurs many years before symptom onset and diagnosis. It is likely that the disease may be too advanced when treatment begins due to diagnostic delay for there to be any significant effect on the disease course. Diagnostic, prognostic, and treatment biomarkers do not yet exist, but they are desperately needed. Medication development is also difficult because there are many hypotheses that explain the pathogenesis – it is difficult to focus on one area specifically. Without a specific pathology target, medication target engagement is uncertain. There are no ideal animal models; SOD1 mutated mice can be used, but they are only useful for determining therapies that target that mutation. Various groups are working to improve the clinical trials process to better determine medication efficacy.[11,12]

There are many clinical trials of ALS treatments ongoing but the percentage of patients participating in clinical trials are surprisingly low at most ALS Clinics. Patients are reluctant to join trials especially those that are placebo controlled.[13] The Northeast ALS (NEALS) consortium has developed a clinical trial design that minimizes use of placebo groups while multiple drugs are simultaneously tested. Clinical trials for ALS symptom management are incredibly important because symptomatic improvement can improve overall QOL in patients with ALS which has no immediate cure, but few of these trials currently exist.

Riluzole (Rilutek®, Tiglutik®) and edaravone (Radicava®) are the two FDA-approved disease modifying treatments for ALS. 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 a benzothiazole given orally that 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 FVC of greater than 60 percent.[14,15] Real-world

data has shown improvements in median survival times of more than 19 months.[16] The AAN practice parameter states that riluzole should be offered to slow disease progression in patients with ALS (Level A evidence).[9] It is probably more effective in the early stages of the disease. Approximately 70 to 80 percent of patients are currently taking riluzole. An annual cost of $25,000 is a primary reason patients are not receiving this medication.

Edaravone (Radicava®) was approved by the FDA in 2017 to slow the functional decline in patients with ALS. Edaravone is an intravenous antioxidant that was studied in two randomized trials in Japan. The first trial in patients within three years of symptom onset showed no benefit over placebo; however, a post-hoc analysis suggested that a subset of patients with a more rapid rate of progression benefitted from treatment with edaravone.[17] The second trial was done on 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. 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 (Exhibit 5).[18] The cost of edaravone is estimated to be around $148,000 per year.

ALS is an expensive disease to manage for both patients and payers. Medical costs are substantial and increase rapidly with each disability milestone. One study found that nine months before diagnosis patients had total annual costs of $10,000, by 15 months after diagnosis the costs were $58,973, and at the time of hospice care the costs were $76,179.[19] Annual direct and indirect cost per patient was estimated to be $69,475 in 2015, which was before the approval of $148,000 annual cost of edaravone.[20] In a case study that collected all expenses related to the cost of care for an individual patient over a 10-year period (2001 to 2010) found that the total disease-duration costs were $1,433,992 (85% paid by insurance, 9% paid by family, 6% paid by charities).[21] The highest costs were for in-home caregivers ($669,150), ventilation ($212,430) and hospital care ($114,558).

Conclusion

Enormous progress in the care and management of ALS has been made in the past 20 years. A combination of disease-modifying therapies, aggressive symptomatic treatment, and nutritional and respiratory care improve overall QOL and prolong survival in patients with ALS. Clinicians caring for these patients need to ensure they stay in the best condition so that if any potential medication is developed, its benefits can be maximized. Maximum efforts have been made to find biomarkers and the cause of ALS. Clinical trials that test only the efficacy of a drug of interest are not ideal, but clinical trials are potentially the best vehicle to conduct appropriate and impactful studies.

Hiroshi Mitsumoto, MD, DSc is the Wesley J. Howe Professor of Neurology at the Eleanor and Lou Gehrig ALS Center at The Neurological Institute of New York and Columbia University Irving Medical Center, New York.

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Recent Advances in Targeted Therapy in the Management of Chronic Lymphocytic Leukemia (CLL): A Closer Look at the Role of Emerging Therapies

Matthew S. Davids, MD, MMSc

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 management of chronic lymphocytic leukemia (CLL) has shifted from chemotherapy or chemoimmunotherapy to oral novel agents. To continue to improve survival in this disease, various combinations of novel agents, novel agents with chemoimmunotherapy, and other new classes of therapy are all under investigation.

Key Points

- Oral novel agents, especially ibrutinib, are the main treatment for CLL.
- Acalabrutinib is a new agent that may be less toxic than ibrutinib.
- Triple and even quadruple therapy regimens are likely to become the standard treatment soon.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) is a chronic lymphoproliferative disorder of monoclonal B cells. There are approximately 20,000 new cases diagnosed every year in the United States (U.S.), with a median age at diagnosis of 72.[1] There will be an estimated 4,060 deaths from CLL in 2020.[2] In 2017, there were an estimated 186,422 people living with CLL in the U.S.[2] The most common presentation is an asymptomatic lymphocytosis that gets identified on routine bloodwork.

There is a tremendous variation in disease course. Higher risk clinical prognostic features for an aggressive disease course are negative β-2 microglobulin, male gender, older age, and short lymphocyte doubling time (LDT). Historical median survival has ranged from 150 months or greater for early stage disease (Rai 0/Binet A) to 19 to 24 months for late stage (Rai III-IV/Binet C). Overall, five-year survival with CLL is 86.1 percent.[2]

Biologic predictors of prognosis include cytogenetic abnormalities (fluorescence in situ hybridization, FISH), immunoglobulin gene mutation (immunoglobulin heavy chain variable region, IGHV), and somatic mutations (NOTCH receptor 1, Notch 1, tumor protein 53, TP53). With FISH abnormalities, 17p and 11q deletion predict shorter survival compared to 12q trisomy, normal FISH, and 13q deletion (as the sole abnormality).[3] Mutated immunoglobulin VH is associated with longer survival compared to unmutated.[4,5] Somatic mutations such as TP53 or NOTCH1 indicate more aggressive disease and thus patients with these mutations require treatment sooner.[6]

Guidelines for the diagnosis and treatment of CLL have been issued by the National Comprehensive Cancer Network (NCCN), the International Workshop on Chronic Lymphocytic Leukemia (iwCLL), and the European Society of Medical Oncology (ESMO).[7-9] The guidelines are in agreement that patients with early stage CLL should not be treated with chemotherapy until they become symptomatic or display evidence of rapid progression of disease and patients at low- risk and intermediate risk (i.e., Rai stages 0-II), who have no indications for treatment, should be monitored every three to 12 months. No survival advantage

Exhibit 1: Indications for Treatment[7]

- Cytopenias (anemia, thrombocytopenia)
- Bulky or rapidly enlarging lymphadenopathy or splenomegaly
- Significant disease-related symptoms (e.g., fatigue, night sweats, weight loss, fever without infection)
- Refractory autoimmune conditions
- +/- lymphocyte doubling time < 6 months

to earlier chemotherapy treatment compared with later treatment has been shown, which led to the watch and wait until symptomatic standard of care.[10] Exhibit 1 shows the indications for treatment.[7]

Once symptomatic, treatment options for CLL include chemoimmunotherapy (chemotherapy + immune mediating therapy) and novel agents which both stop or slow the growth of CLL cells throughout the body. Some patients with high-risk disease may be referred for stem cell transplant even before becoming symptomatic. Treatment is chosen based on histologic and genetic testing results and patient characteristics (age, functional status, comorbidities).

A modern era trial of chemoimmunotherapy (fludarabine, cyclophosphamide, and rituximab (FCR) found no significant overall survival benefit for treating early stage high-risk patients with early therapy compared to waiting.[11] The author concluded that although FCR is efficient in inducing remissions in the early stage high-risk CLL, the data do not provide evidence that alters the current watch and wait standard of care for these patients.

The treatment of CLL underwent considerable changes with the introduction of orally administered, well-tolerated kinase-inhibitors such as ibrutinib, a potent inhibitor of Bruton's tyrosine kinase (BTK). Approved novel targeted agents in CLL are mechanistically diverse and, in addition to ibrutinib, they include acalabrutinib (second-generation BTK inhibitor), obinutuzumab (anti-CD20 monoclonal antibody), idelalisib (PI3K inhibitor), duvelisib (PI3K inhibitor), and venetoclax (BCL-2 inhibitor). Ibrutinib was approved by the FDA in 2014 and is preferred first-line therapy (category 1) in the NCCN guidelines for those without del(17p)/TP53 mutation.[7] Toxicities of note with this agent are bleeding, dysrhythmia, arthralgias, hypertension, and rash. CLL12 is the first prospective, multicenter, placebo-controlled, double-blind, Phase III study to compare efficacy and safety of ibrutinib to a watch-and-wait approach in Binet stage A CLL with risk of disease progression defined by the comprehensive CLL score. At a median observation time of 31 months, event-free survival was 47.8 months in the placebo arm versus not reached in the ibrutinib arm (hazard ratio [HR] = 0.25, 95% confidence interval [CI] = 0.14 to 0.43; $p < .0001$).[12] Progression-free survival was 14.8 months in the placebo arm versus not reached in the ibrutinib arm (HR = 0.18, 95% CI = 0.12 to 0.27). Time to next treatment was longer in the ibrutinib arm. Event-free survival, progression-free survival, and time to next treatment were consistent across all risk groups, except for exceedingly high–risk patients (due to small numbers). Final data on this trial has not yet been published.

Obinutuzumab, FDA approved in 2013, is a humanized type II anti-CD20 monoclonal antibody given intravenously that binds to the CD20 antigen, a proven target for CD20+ B cells. Its mechanism of action is thought to be antibody-dependent cellular cytotoxicity (ADCC), direct B-cell death, and complement-dependent cytotoxicity. It was engineered to be more effective than rituximab, another anti-CD20 monoclonal antibody. Toxicities of note with this agent are infusion reactions, neutropenia, and infection. It is a preferred option in combination with acalabrutinib or venetoclax as first-line therapy in CLL with and without del(17p)/TP53 mutation.[7]

Venetoclax, approved in 2015, is highly active in CLL. It is used in combination with obinutuzumab for first-line therapy and with rituximab for relapsed/refractory disease. Tumor lysis syndrome (TLS) is an important, but manageable risk with this agent. TLS is hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia because of rapid destruction of cancer cells. Slow dose increases over a month and good hydration significantly reduce the risk. Other toxicities of note with venetoclax are neutropenia and gastrointestinal disturbances.

Idelalisib and duvelisib are both PI3K inhibitors that are FDA approved for treating relapsed/refractory CLL. Duvelisib, an oral PI3K-δ/γ dual inhibitor, is approved for relapsed/refractory CLL after two or more prior lines of therapy and is used as monotherapy. Idelalisib has the same indication and is used in combination with rituximab. Toxicities of note with this class are diarrhea/colitis, transaminitis, and pneumonitis. Duvelisib can also cause cutaneous reactions.

Acalabrutinib is the first of the next-generation BTK inhibitors to be approved for use. It was FDA approved for treatment of CLL as first-line or subsequent line in November of 2019. It is a

Exhibit 2: Factors to Consider in Selecting Between Front-Line Agents in Frail Older Patients

Ibrutinib	Venetoclax/Obinutuzumab
• Long-term efficacy data	• Potential for 1-year time-limited therapy
• Convenience (no infusions, TLS monitoring)	• No known cardiac or bleeding risks
• Phase III data compared to FCR and BR	• Less concern for long-term adherence
• Category 1 first-line therapy for those without del(17p) or T53 mutation (NCCN)	• Potential for cost-saving if 1-year of therapy is durable
• More data for efficacy of venetoclax at time of ibrutinib progression	

Acalabrutinib with or without Obinutuzumab
• Less efficacy data
• Fewer major adverse events of acalabrutinib compared to ibrutinib

TLS = tumor lysis syndrome; FCR = fludarabine/cyclophosphamide/rituximab;
BR = bendamustine/rituximab; NCCN, National Comprehensive Cancer Network

Exhibit 3: Inhibiting Three Distinct Targets Has the Potential for Even Greater Efficacy[14]

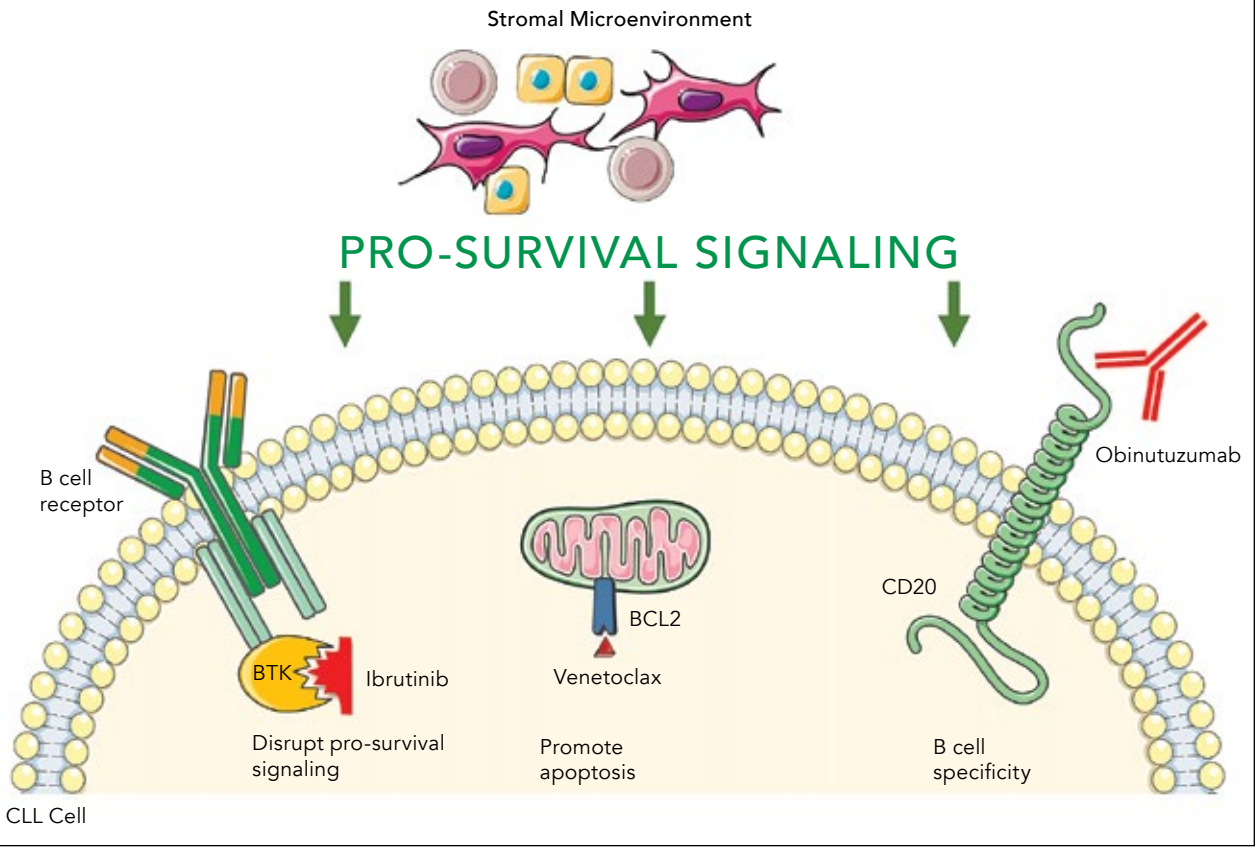

Exhibit 4: Selected Trials of CD19-Targeted CAR T-Cells in CLL[16-21]

	Number of Patients with CLL	Costimultory Domain	ORR n, (%)	CR n, (%)
	8	**CD-28**	**7/8 (87%)**	**4/8 (50%)**
CAR-T Alone	14	4-1BB	8/14 (58%)	4/14 (29%)
	13	4-1BB	4/13 (31%)	1/13 (8%)
	17	4-1BB	9/17 (53%)	6/17 (35%)
	24	4-1BB	14/19 (74%)	4/19 (21%)
	23	4-1BB	18/22 (82%)	10/22 (46%)
CAR-T + ibrutinib	14	4-1BB	10/14 (71%)	6/14 (43%)
	17	4-1BB	14/16 (88%)	NR

ORR = objective response rate; CR = complete response

highly selective, potent kinase inhibitor that was designed to minimize off-target activity with minimal effects on TEC, EGFR, or ITK signaling. Its greater selectivity is expected to reduce major adverse events seen with ibrutinib. Compared to ibrutinib, there are some overlapping toxicities including mild diarrhea, mild bleeding, and infections. Unique toxicities with acalabrutinib are headache and weight gain. Less commonly seen with acalabrutinib than ibrutinib are atrial fibrillation, major hemorrhage, significant skin toxicity, and pneumonitis. No ventricular arrhythmias were reported in the premarketing studies.

Exhibit 2 shows some factors clinicians can consider in choosing between ibrutinib, acalabrutinib with or without obinutuzumab, or venetoclax/obinutuzumab for front-line therapy in older, frail patients.

The main limitations of novel agent monotherapy in the first line are achievement of complete response and undetectable minimal residual disease (MRD) is rare. Duration of response in del(17p) is short. Resistance mutations against the novel agents also occur, leading to relapse. Ongoing toxicities, long-term adherence issues, and cost also limit first-line therapy.

Time-limited combination therapy may be a solution. Ibrutinib in combination with fludarabine, cyclophosphamide, and rituximab (iFCR) is a new front-line regimen that results in deep remissions in non-TP53 aberrant CLL. FCR can improve disease-free survival for younger (age ≤65 years) fit patients with CLL with mutated IGHV. However, patients with unmutated IGHV rarely have durable responses with FCR. Ibrutinib is active for patients with CLL irrespective of IGHV mutation status but requires continuous treatment. In the trial of this triple combination ibrutinib was given orally (420 mg/day) for seven days, then up to six 28-day cycles were administered intravenously of FCR with continuous oral ibrutinib (420 mg/day). Responders continued ibrutinib maintenance for up to two years, and patients with MRD in bone marrow after two years were able to discontinue treatment. MRD was achieved in 71 of 85 patients (84%) .[13]

Inhibiting three distinct targets has the potential for even greater efficacy than monotherapy or dual therapy (Exhibit 3).[14] The triple combination of ibrutinib, venetoclax, and obinutuzumab was well-tolerated and active in relapsed/refractory CLL.[15] Cooperative group studies are ongoing to help determine if triple therapy might become the new standard of care for first-line CLL treatment.

Therapeutic options for CLL patients will likely show much improvement soon. Additional agents are under investigation in the current drug classes, including zanubrutinib, vecabrutinib, ARQ-31, umbralisib, MEI-401, and cirmtuzumab. Other treatment approaches including myeloid cell leukemia-1 (MCL-1) inhibitors, antibody-drug conjugates (ADCs), and CAR-T are also being studied. MCL-1 is an anti-apoptotic member of the BCL-2 family of proteins that regulates apoptosis. Elevated levels of MCL-1 contribute

to tumorigenesis and resistance, not only to conventional chemotherapies but also to targeted therapies, including the BCL-2 selective inhibitor venetoclax.

CAR-T is a novel approach involving the use of engineered autologous T cells and has shown success in the treatment of CLL. Patients' own T cells are harvested by leukapheresis, then manipulated to express a chimeric antigen receptor (CAR) thereby combining antibody-mediated targeting and cell-mediated killing in a single therapeutic strategy. A CAR directed against CD19 is first introduced (usually via lentiviral or retroviral transduction) into autologous T cells and these cells are expanded ex vivo over two weeks prior to intravenous infusion. Numerous trials of CAR-T with or without ibrutinib have been published (Exhibit 4).[16-21]

Conclusion

There is now a powerful toolkit of novel agents, with more coming and there is still a limited role for chemoimmunotherapy in managing CLL. Novel agent monotherapy may be best for frail or low-risk patients. Fit patients (especially those with high risk markers) may benefit from combination therapy. The optimal combination strategies and sequences are yet to be defined thus active investigation with clinical trials remains critical.

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Informed Decision-Making in the Treatment and Management of Chronic Heart Failure: Expert Strategies for Improved Patient Outcomes

Biykem Bozkurt, MD, FACC, FAHA, FHFSA

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 numerous strategies that can be used to improve patient outcomes in those with heart failure (HF). Guideline-directed medical therapy, especially including newer agents, disease management programs, multidisciplinary teams, and promotion of medication adherence are all important in reducing death and hospitalizations.

Key Points

- Sacubitril/valsartan reduces the risk of death and hospitalization for HF more than enalapril and is an option for first-line HF treatment.
- Clinicians should consider switching patients who tolerate an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) to sacubitril/valsartan.
- Sodium-glucose cotransporter -2 (SGLT-2) inhibitors should be considered in patients with diabetes and HF, and possibly even in those without diabetes.
- HF disease management programs have been shown to reduce readmission risk by 25 percent.

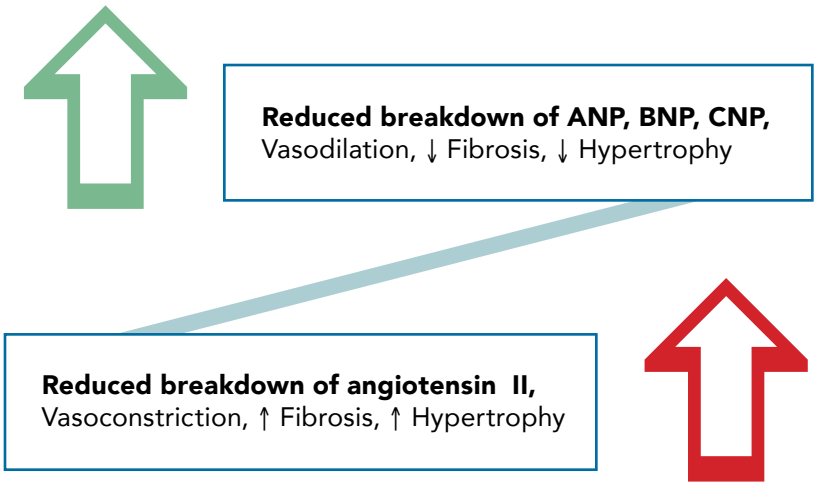
THE PREVALENCE OF HEART FAILURE (HF) in the United States (U.S.) continues to rise over time, with aging of the population. An estimated 6.2 million American adults over 20 years of age had HF between 2013 and 2016, compared with an estimated 5.7 million between 2009 and 2012.[1] Projections show that the prevalence of HF will increase 46 percent from 2012 to 2030, resulting in more than eight million people with HF. Additionally, the total percentage of the population with HF is predicted to increase from 2.42 percent in 2012 to 2.97 percent in 2030.

HF can be divided into HF with reduced ejection fraction (HFrEF), which is the focus of this article, and HF with preserved ejection fraction (HFpEF). These are each treated differently. The American Heart Association, American College of Cardiology, and the Heart Failure Society of American (AHA/ACC/HFSA) published updated guidelines for managing HFrEF in 2017.[2] Treatment recommendations for HFrEF are based on the classification of HF from Stage A to D.[2] For example, a patient with shortness of breath and fatigue and reduced exercise tolerance would be Stage C, and Stage D is end-stage disease.

The pathophysiology of heart failure involves a maladaptive response during which the renin-angiotensin-aldosterone system (RAAS) is activated. RAAS activation leads to vasoconstriction, hypertension, increased aldosterone levels, increased sympathetic tone, and eventually, cardiac remodeling. By blocking these maladaptive elements, an ACE inhibitor or an ARB plays a major role in reducing morbidity and mortality due to heart failure.

The natriuretic peptide system is also activated in HF; this is a compensatory mechanism that leads to vasodilation, natriuresis and diuresis, lowered

Exhibit 1: Balance of Neprilysin Inhibition[3]



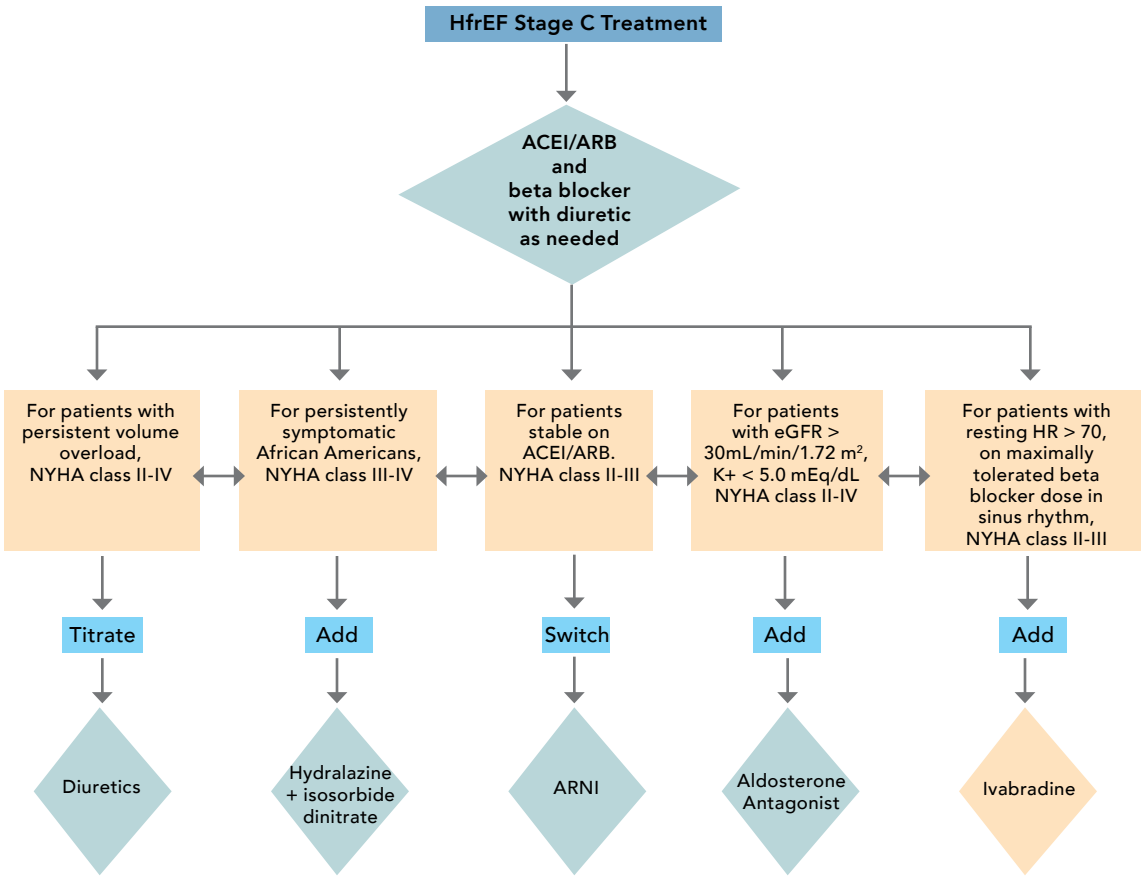
NEP = neprilysin; ANP = atrial natriuretic peptide;
BNP = brain natriuretic peptide, CNP = C type natriuretic peptide

blood pressure, lowered sympathetic tone, and reduced aldosterone levels. The natriuretic peptide system works antagonistically to the RAAS and has favorable effects on the pathogenesis of heart failure. Natriuretic peptides, atrial natriuretic protein (ANP) and brain natriuretic protein (BNP) are broken down by neprilysin. Neprilysin (NEP) is also responsible for the breakdown of other substances, including bradykinin and angiotensin II.

NEP inhibition alone may result in upregulation and potentiation of beneficial peptides, such as ANP and BNP, as well as maladaptive peptides, such as angiotensin II (Exhibit 1).[3] The antihypertensive effects may be offset by increased activity of the RAAS and sympathetic nervous system and/or by downregulation of ANP receptors. Thus, NEP inhibitors must be given with inhibitors of angiotensin II such as valsartan. Sacubitril is the first approved NEP inhibitor and is marketed in combination with valsartan (Entresto®) as an angiotensin receptor neprilysin inhibitor (ARNI). In the PARADIGM-HF study, sacubitril in combination with valsartan was superior to enalapril in reducing the risks of death and of hospitalization for HF. The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit with sacubitril/valsartan had been crossed. The primary outcome had occurred in 21.8 percent in the sacubitril/valsartan group and 26.5 percent in the enalapril group ($p < 0.001$).[4] A total of 17.0 percent and 19.8 percent, respectively, died (hazard ratio for death from any cause, 0.84; 95 percent confidence interval CI, 0.76 to 0.93; $p < 0.001$); of these patients, 13.3 percent and 16.5 percent, respectively, died from cardiovascular causes (hazard ratio, 0.80; 95 percent CI, 0.71 to 0.89; $p < 0.001$). Sacubitril/valsartan also reduced the risk of hospitalization for HF by 21 percent ($p < 0.001$) and decreased the symptoms and physical limitations of HF ($p = 0.001$). The rates of hypotension and nonserious angioedema were higher in the sacubitril/valsartan group; however, there were lower rates of renal impairment, hyperkalemia, and cough than in the enalapril group.

Guideline-directed medical therapy (GDMT) has been shown to improve outcomes in those with HF. Inhibition of the renin-angiotensin system with an ACE inhibitor or ARB can prevent progression from Stage A or B to symptomatic HF. Beta blockers, in addition to an ACE inhibitor and ARB are appropriate for some patients at Stage B. For Stage C, an ACE inhibitor (Level of evidence [LOE]:A), or ARBs (LOE: A), or ARNI (LOE: B-R) in conjunction with evidence-based beta blockers and aldosterone antagonists in selected patients, is recommended for patients with chronic HFrEF to reduce morbidity and mortality.[2] In addition to recommended ARNI as an option for HFrEF as initial therapy, the guidelines state that in patients

Exhibit 2: Management of Stage C HFrEF[2]

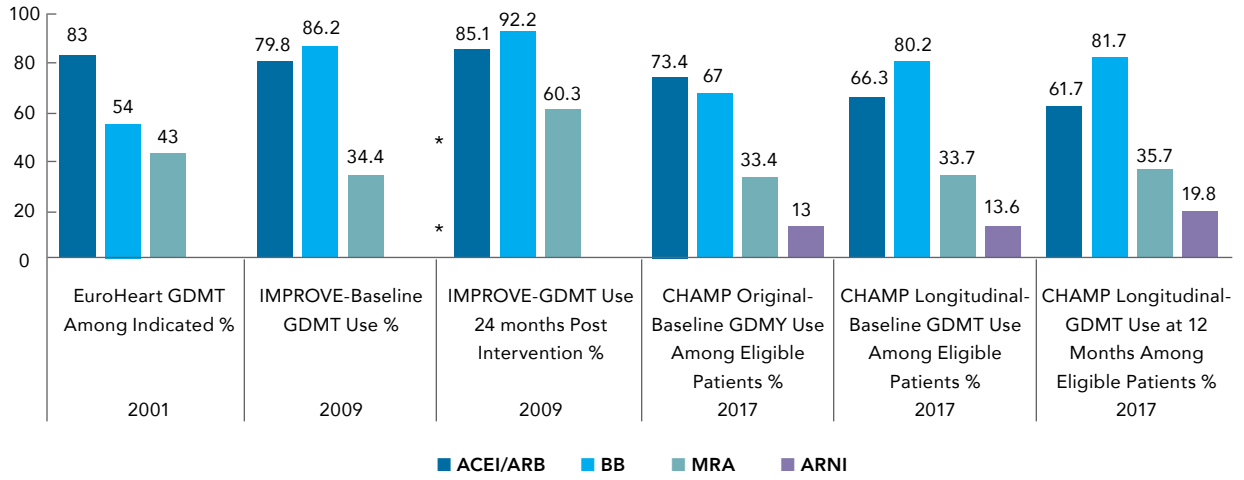


with chronic symptomatic HFrEF, New York Heart Association (NYHA) class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.[2] Importantly, to prevent angioedema, ARNI should not be administered concomitantly with an ACE inhibitor, or within 36 hours of the last dose of an ACE inhibitor. Additionally, ARNI should not be administered to patients with a history of angioedema.

Ivabradine is a specific and selective inhibitor of the funny current (I_f) ion channel. The I_f is highly expressed in spontaneously active cardiac regions, such as the sinoatrial node, the atrioventricular node, and the Purkinje fibers of conduction tissue. The I_f is a mixed sodium–potassium current that activates upon hyperpolarization. It controls the rate of spontaneous activity of sinoatrial myocytes, hence the cardiac rate. Raised resting heart rate is a risk factor for adverse outcomes with HF and thus was the reason for investigating this agent. In the SHIFT trial, 24 percent of the ivabradine group and 29 percent of those taking placebo had a primary endpoint event (composite of cardiovascular death or hospital admission for worsening HF, $p < 0.0001$).[5] The effects were driven mainly by hospital admissions for worsening HF (16% versus 21%; $p < 0.0001$) and deaths due to HF(3% versus 5%, $p = 0.014$). The subjects in this trial were NYHA II–IV with EF < 35 percent and a heart rate of ≥ 70 beats per minutes. Ninety percent were on a β-blocker (90%), but only 25 percent of those were on full dose. Bradycardia is the most common adverse event with this agent. The guidelines state that ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (EF ≤ 35%) who are receiving GDMT, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest.[2] Exhibit 2 summarizes the suggested treatment of Stage C HfrEF.[2]

Managing HF also requires management of comorbid diseases which can exacerbate HF,

Exhibit 3: Prescription Rates for Heart Failure Medications in Heart Failure Registries[15]



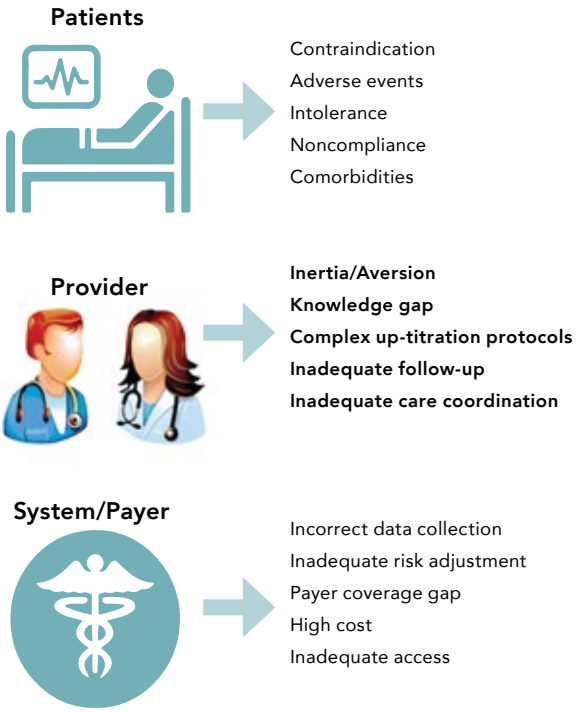
including hypertension, anemia, and sleep apnea. For hypertension, the goal is to achieve a systolic blood pressure less than 130. For most patients, the typical HF medications are sufficient to achieve this level. For anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality. In patients with NYHA class II and III HF and iron deficiency (ferritin < 100 ng/mL or 100 to 300 ng/mL if transferrin saturation is < 20%), intravenous iron replacement might be reasonable to improve functional status and quality of life.[2,6] For patients with HF and suspected sleep apnea, a formal sleep assessment should be done. Continuous positive airway pressure (CPAP) therapy may be reasonable to improve sleep quality and daytime sleepiness for those identified with sleep apnea. The guidelines note that for patients with NYHA class II–IV HFrEF and central sleep apnea, adaptive servo-ventilation causes harm.[2]

Poor glycemic control is associated with incident HF; a Kaiser study found that for every 1 percent increase in hemoglobin A1C there was an 8 percent increased risk of HF.[7] The SGLT-2 inhibitors, a newer class of anti-diabetic agents, cause a mild natriuretic diuretic effect and result in weight loss, in addition to decreasing serum glucose by increasing renal excretion of glucose. The three available agents in this class are canagliflozin, dapagliflozin, empagliflozin. Weight is reduced by approximately 2 kg with SGLT-2 inhibitors. HF hospitalizations are significantly reduced by these agents in patients with type 2 diabetes, those at high risk for cardiovascular disease (CVD) and/or those who already have CVD.[8-10] The 2016 European Society of Cardiology HF guidelines recommend that empagliflozin should be considered in patients with type 2 diabetes with Stage A HF to prevent or delay onset of HF and prolong life; only empagliflozin is included in these guidelines because the trial with canagliflozin had not yet been published.[11]

In a randomized trial of patients with HFrEF, dapagliflozin added to recommended therapy significantly reduced the risk of worsening HF or cardiovascular death independent of diabetes status compared to placebo.[12] Several studies with various other anti-diabetic classes have been conducted in patients with diabetes with high cardiovascular risk demonstrating differences in HF risk; the dipeptidyl peptidase 4 (DPP4) inhibitors, specifically saxagliptin, have been associated with increased HF risk, and the glucagon-like peptide (GLP-1) agonists did not have any significant effect on risk. There are several trials ongoing with the SGLT-2 inhibitors in HFrEF with elevated BNP levels. Clinicians can consider adding a SGLT-2 inhibitor to patients' regimens even if they do not have diabetes.

Reducing HF hospital readmissions is a common goal for many managed care plans. HF disease management programs have been shown to reduce readmission risk. Across 10 studies, the effect is a 25 percent reduction in risk.[13] A multidisciplinary team managing HF patients also has an impact on hospitalizations in general and mortality. The guidelines recommend multidisciplinary HF disease-management programs to reduce hospital readmission for patients at high risk, to facilitate the implementation of GDMT, to address different barriers to behavioral change, and to reduce the risk of subsequent rehospitalization for HF.[2] It is important to have close communication at the time

Exhibit 4: Reasons for Treatment Gap[15]



of hospital discharge between the inpatient and outpatient setting. An early follow-up visit (within 7 to 14 days) and early telephone follow-up (within 3 days) of hospital discharge is reasonable to help ward off readmission.

Effective systems of care coordination with special attention to care transitions should be deployed for every patient with HF that facilitate and ensure effective care that is designed to achieve GDMT and prevent hospitalization. Every patient with HF should have a clear, detailed and evidence-based plan of care that ensures the achievement of GDMT goals, effective management of comorbid conditions, timely follow-up with the healthcare team, appropriate dietary and physical activities, and compliance with secondary prevention guidelines for cardiovascular disease. This plan of care should be updated regularly and made readily available to all members of each patient's healthcare team.

Medication adherence and persistence are an issue with HF, and affordability of all the various medications that can be required to manage HF can also be an issue. Many of the ACE inhibitors, ARBs and beta blockers are generic, but there can be wide variability in the pricing of generics.[14] Clinicians need to stress adherence at each visit and work with the patient to identify and overcome barriers that prevent adherence.

Despite increased awareness with recommendations, in practice guidelines and performance measures, little progress in the proportion of patients treated with GDMT, or patients achieving target doses of HF medications, has been made in the past two decades.[15] Specifically, rates for ACE inhibitor or ARB use have not increased in the last 18 years according to population-based HF registries (Exhibit 3).[15] Sixty-one to 78 percent of patients receive an ACE inhibitor or an ARB. There are several reasons hypothesized for this lack of improvement, including provider aversion and inertia, patient intolerance and adverse events, lack of payer or insurance coverage, and data and cost limitations. Exhibit 4 shows these divided out by patient, provider, and payer specific issues.

Conclusion

Managing HF with reduced ejection fraction that is Stage C or later can be a daunting task which requires numerous different medications and a multidisciplinary team disease management approach. To achieve the best outcomes, patients need to receive GDMT including achieving target doses for each therapy. Newer advances in HF treatment include ARNI and SGLT-2 inhibitors to reduce risk and improve outcomes.

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Patient-Focused Treatment Decisions in Metastatic Melanoma: An In-Depth Look at the Role of Checkpoint Inhibitors

Ragini R. Kudchadkar, 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

Checkpoint inhibitor-based immunotherapy treatment is making a difference in the survival of metastatic melanoma and improving relapse-free survival in earlier stages of the disease. Choosing to treat a patient with adjuvant immunotherapy after surgical removal of Stage III disease requires an evaluation of recurrence risk and immune-related adverse events of immunotherapy.

Key Points

- Immunotherapy is the first-line therapy for metastatic disease.
- It is also now an option as adjuvant therapy after surgical removal in certain stages.
- Immune-related adverse events must be considered in choosing immunotherapy.

CHECKPOINT INHIBITOR IMMUNOtherapy is an important intervention in the treatment of melanoma. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors and programmed death one (PD-1) inhibitors are the two available classes of checkpoint inhibitor immunotherapy with FDA approvals for treating melanoma.

PD-1 inhibitors (pembrolizumab and nivolumab) and CTLA-4 inhibition (ipilimumab) takes the brakes off T-cell activation (Exhibits 1 and 2). Tumors express programmed death-ligand 1 (PD-L1) which binds on T cells which turns them off. Blocking PD-1 or PD-L1, in the case of other immunotherapies not used in melanoma, allows T cells to remain active against tumors. CTLA-4 is a protein receptor that functions as an immune checkpoint and downregulates immune responses.[1] CTLA-4 is constitutively expressed in regulatory T cells, but only upregulated in conventional T cells after activation. It acts as an "off" switch when bound to CD80 or CD86 on the surface of antigen-presenting cells; blocking CTLA-4 interaction allows T cells to remain active. Immunotherapy is essentially taking the brakes off the immune system, which can sometimes lead to an overactive immune system that causes immune-related adverse events. The National Comprehensive Cancer Network (NCCN) guidelines for cutaneous melanoma recommend immunotherapy as adjunctive therapy after initial surgical removal for stages of melanoma with positive sentinel nodes and after localized treatment of recurrence, and as first-line systemic therapy for metastatic disease (Stage IV).[2]

The five-year survival rates for resected melanoma are 93 percent for Stage IIIA, 83 percent for Stage IIIB, 69 percent for Stage IIIC, and 32 percent for Stage IIID.[3] The place for adjunctive immunotherapy after surgical removal is likely for those with Stage IIIB or worse, although a few Stage IIIA patients were included in the trials. For adjunctive therapy, nivolumab and pembrolizumab improve relapse-free survival (RFS) in those with Stage III disease; overall survival data have not yet been reported.[4,5] If a patient's tumor has a BRAF V600 activating mutation, BRAF/MEK combination therapy is recommended instead of immunotherapy. Ipilimumab alone may be an option in cases where the patient has already been treated with anti-PD-1 therapy, but the RFS is lower than with the other two agents. The role of combination

Exhibit 1: PD-1 and PD-L1 Blockade

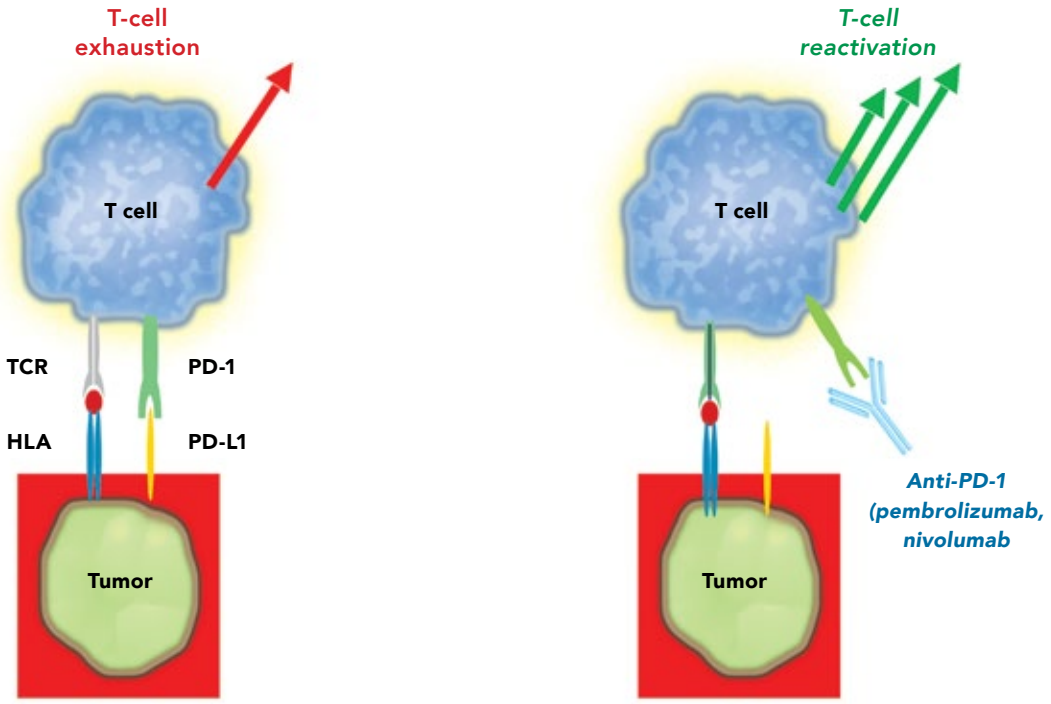
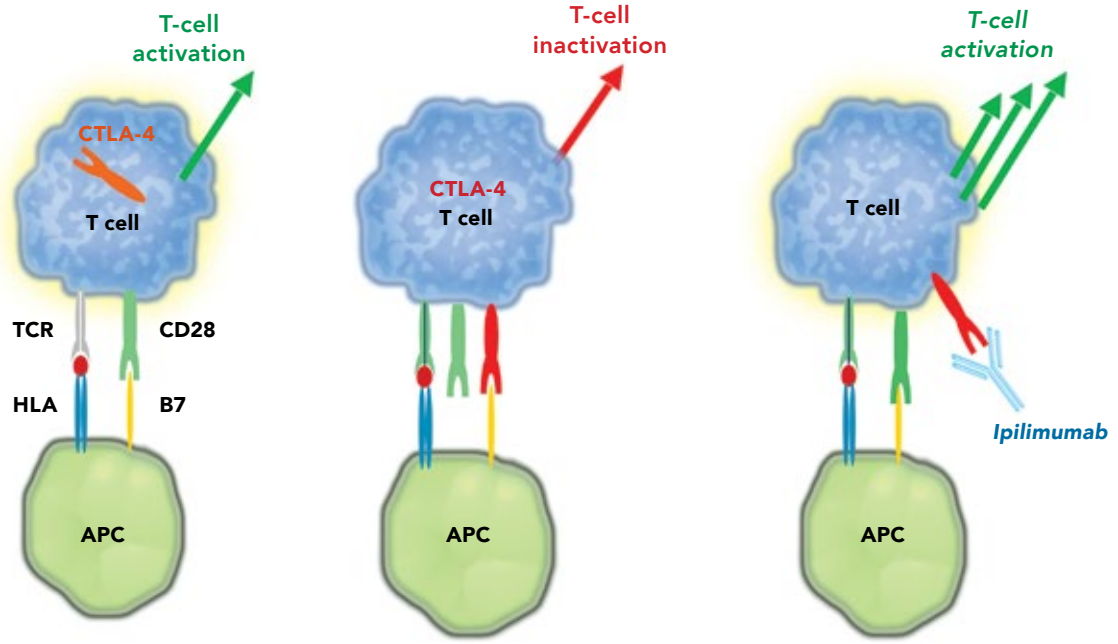


Exhibit 2: CTLA4 Blockade: Taking the Brakes Off T-Cell Activation



APC = antigen-presenting cell

Exhibit 3: Symptomatic MBMs[11-14]			
Treatment	**Patients**	**ORR**	**DOR**
Ipilimumab	21	5%	Not reported
Nivolumab	16	6%	Not reached
Ipilimumab + Nivolumab	18	22%	Not reported
Dabrafenib + Trametinib*	17	59%	4.5 months

*BRAF V600 mutation

nivolumab/ipilimumab in the adjuvant setting is not yet known. Choosing adjuvant therapy versus observation is based on evaluation of individualized patient risk of recurrence compared to the risks of treatment, especially the irreversible endocrine immune-related adverse events (i.e., type 1 diabetes, hypothyroidism).

Metastatic melanoma is an aggressive cancer with a low survival rate. By harnessing the surveillance and cytotoxic features of the immune system, immunotherapies can provide a durable response and improve disease outcomes in patients with metastatic melanoma. Close monitoring is necessary, however, to identify and treat immune system-related adverse events before they become life-threatening. Immunotherapy with pembrolizumab, nivolumab, and nivolumab/ipilimumab are all category 1 recommendations for first-line therapy for metastatic disease, unless a BRAF V600 activating mutation is present for which BRAF/MEK combinations are recommended.[2] Immunotherapy has led to a significant portion of patients with metastatic disease being alive at five years; the figures are 34 percent for pembrolizumab (41% for immunotherapy naïve), 44 percent for nivolumab, and 52 percent for nivolumab/ipilimumab.[6,7] In the not-too-distant past, overall five-year survival for patients with metastatic melanoma was in the range of 5 to 10 percent. Importantly, these figures for pembrolizumab and nivolumab containing regimens are not from a direct comparison trial. Although it would appear that survival rates are better with combination immunotherapy, the rates of immune-related adverse events and treatment discontinuation because of the adverse events are also higher for nivolumab/ipilimumab compared to immunotherapy with a single agent; some patients are not able to tolerate the combination.

Melanoma is the most common cancer that metastasizes to the brain.[8] More than half of metastatic melanoma patients will have central nervous system (CNS) involvement during their disease. Historically, overall survival for CNS disease was four to five months. Surgery, stereotactic radiosurgery, and whole brain radiation have been the standard of care, but immunotherapy has now been investigated in asymptomatic patients not requiring steroids. Single-agent ipilimumab has a CNS overall response rate (ORR) of 16 percent. Both nivolumab and pembrolizumab have a CNS ORR of 20 percent, and ipilimumab/nivolumab has a response rate of 55 percent.[9,10] Exhibit 3 compares the efficacy from small trials in those with symptomatic brain metastases.[11-14] The combination of ipilimumab/nivolumab or BRAF/MEK, for BRAF V600 mutation, are the better choices rather than single-agent immunotherapy in the case of symptomatic brain metastases. Symptomatic brain metastases are treated with corticosteroids, which seems to decrease the efficacy of immunotherapy when the patient has been receiving them before starting immunotherapy.

Conclusion

For patients with Stage III and IV melanoma, treatment and survival have drastically improved over the past five years. Anti-PD-1immunotherapies have shown improvement in RFS in the adjuvant setting; however, overall survival benefit and the role of combination nivolumab/ipilimumab are not yet known. Immunotherapy improves overall survival in Stage IV melanoma, but the best sequencing of immunotherapy and BRAF/MEK inhibitors, when both are an option, is not yet known. Brain metastases, symptomatology from cancer or comorbidities, and potential risks of immunotherapy are key to decision-making. Studies are ongoing looking at combination immunotherapy and BRAF/MEK inhibitors; early results have shown significant toxicity and long-term follow-up data are needed.

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New Frontiers in the Treatment of Acute Myeloid Leukemia (AML): Patient-Centric Navigation in the Age of 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

The management of acute myeloid leukemia (AML) has dramatically changed in recent years with the introduction of oral once-a-day targeted agents. Understanding of the genetic mutations which drive this disease has led to this growing list of therapies. These therapies are improving survival while allowing patients to primarily be treated on an outpatient basis.

Key Points

- There are several targeted therapies for various genetic mutations found in AML.
- The goal is to induce remission and hopefully get the patient to stem cell transplant, which is a potential cure.
- The targeted medications in combination with aggressive chemotherapy regimens have led to significant improvements in survival in younger patients.
- Survival improvements have not been as significant in those older than 60 or those in frail health.

ACUTE MYELOID LEUKEMIA (AML) IS unbridled proliferation of hematopoietic stem cells from the myeloid lineage resulting in marrow failure and patient death unless successfully treated. The risk factors for developing AML are age, prior chemotherapy for other cancers, ionizing radiation, and industrial solvents. Age is the major risk factor, with the other three exposures accounting for less than 10 percent of the incidence. There are approximately 15,000 new cases annually in the United States (U.S.). AML can be de novo or secondary (prior myelodysplastic syndrome (MDS), myeloproliferative disorder, or exposure to potentially leukemogenic therapies or agents). The median age of AML onset is approximately 70 years; however, AML affects all age groups.

A complex interplay of genetic events contributes to AML pathogenesis in individual patients. In adult *de novo* AML, mutations are found in one of nine

Exhibit 1: Key Prognostic Data in AML[2]

Patient **age and history**	
Cytogenetics (screen for rare types of AML - APL, MLL, Ph+, CBF)	
Multiparameter flow	
Molecular studies:	
• **FLT3 ITD mutation**, RUNX1, TP53, ASXL1	***Unfavorable***
• **NPM1 mutation**, **CEBPA biallelic mutation**	***Favorable***

APL = acute promyelocytic leukemia; MLL = mixed lineage leukemia; Ph+ = Philadelphia chromosome; CBF = core binding factor; FLT3 ITD = FMS-like tyrosine kinase-3 internal tandem duplication; RUNX1 = Runt-related transcription factor 1; TP53 = tumor protein 53; ASXL1 = additional sex combs like 1NPM1, nucleophosmin, CEBPA, CCAAT/enhancer binding protein α

Exhibit 2: Risk Stratification in AML[4,5]

Genetic Risk Group	Frequency	Survival	Subset
Favorable	15%	65%	• t(8;21)(q22;q22); *RUNX1-RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* • Mutated *NPM1* without *FLT3*-ITD or *FLT3*-ITD ^{low} • Biallelic Mutated *CEBPA*
Intermediate	55%	50%	• Mutated *NPM1* and *FLT3*-ITD ^{high} • Wild-type *NPM1* without *FLT3*-ITD or *FLT3*-ITD ^{low} (without adverse-risk genetic lesions) • Wild-type *NPM1* and *FLT3*-ITD (normal karyotype) • t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* • Any cytogenetics not classified as favorable or adverse
Adverse	30%	20%	• t(6;9)(p23;q34); *DEK-NUP214* • t(v;11)(v;q23); *KMT2A* rearranged • Inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1 (GATA2, MECOM (EVI1)* • t(9;22)(q34.1;q11.2) BCR-ABL1 • Monosomy 5 or del(5q); monosomy 7; monosomy 17; abnormal 17p • Complex karyotype(≥ 3 abnormalities) or monosomal karyotype • Wild-type *NPM1* and *FLT3*-ITD ^{high} • Mutated *RUNX1* • Mutated *ASXL1* • Mutated *TP53*

categories of genes, including transcription-factor fusions (18% of cases), genes for nucleophosmin (NPM1, 27%), tumor suppression (16%), DNA-methylation (44%), signaling (59%), chromatin-modifying (30%), myeloid transcription factor (22%), cohesin complex (13%), and spliceosome complex (14%).[1] Various factors, including mutations that are present, have classification and prognostic implications (Exhibit 1).[2] For example, FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD^{high}) is a driver mutation that presents with a high leukemic burden, confers a poor prognosis, and has a significant negative impact on the management of patients with AML.[3] Exhibit 2 shows the three genetic/cytogenic risk groups into which AML can be classified and the impact on survival.[4,5]

The general treatment goals with AML are shown in Exhibit 3. Key endpoints of importance in AML are overall survival (OS), event-free survival (EFS, events are defined as no complete remission, relapse, or death), and complete remission (CR) rates. EFS is somewhat correlated with OS and has intrinsic value to patients; when patients have no events, they are in CR with acceptable counts. CR with incomplete platelet or absolute neutrophil (CRi) recovery has value, but CR with minimal residual disease (MRD) has the most value. Having undetectable MRD results in higher OS and lower relapse rates compared to positive MRD.[6]

Acute promyelocytic leukemia (APL) is an aggressive type of AML in which there are too many promyelocytes in the blood and bone marrow. It is caused by a mutation that is acquired over a person's lifetime, usually involving a translocation between chromosomes 15 and 17 [t(15;17)]. Treatment may include the use of all-trans retinoic acid (ATRA) in combination with arsenic trioxide or anthracycline-based chemotherapy (daunorubicin or idarubicin). The risk of death is greatest in the first two weeks after diagnosis, especially if ATRA initiation is delayed. If the clinical setting suggests the possibility of APL, clinicians should not wait for molecular confirmation to start ATRA.

Treatment options for AML comprise a variety of chemotherapy regimens, biologics, targeted agents,

Exhibit 3: General Treatment Goals

- Induction therapy to reduce gross leukemia to undetectable levels (2-3 log cell kill); to achieve complete response (CR) (no AML, normal CBC).
- Reduce 10^9 - 10^{10} cells, undetectable by standard means, present at complete response, to a level low enough to achieve prolonged disease-free survival ('cure').

and stem cell transplantation (SCT). In patients less than 60 years old, AML is treated with aggressive induction chemotherapy regimens to achieve disease remission. The typical chemotherapy is idarubicin or daunorubicin combined with cytarabine given as induction. When CR is achieved, additional therapies are given post-remission as consolidation therapy to reduce risk of relapse in certain cases. Post-remission those with intermediate or adverse-risk disease should receive an allogenic SCT and others may receive additional cytarabine. Targeted therapies are added to chemotherapy based on cytogenetics of the AML or are used instead of chemotherapy in older or poor performance status (unfit) patients.

The survival of those over 60 years of age with AML has improved only modestly since the 1970s compared with survival for those less than 60 years. There are many reasons for the poor survival of those over 60 years, including decreased host tolerance of intensive therapy and increased resistance of disease to therapy. Older patients have an impaired hematopoietic stem cell reserve, a higher rate of comorbid diseases, and a decreased chemotherapy clearance because of impaired kidney and liver function. AML in those over 60 years tends to be more resistant to treatment with a higher ratio of unfavorable cytogenetics, a higher expression of drug resistance proteins (e.g., P-glycoprotein), and a higher incidence of antecedent hematologic disorders. Secondary AML and TP53-mutated disease are both associated with lower survival rates in those over 60 years.[7] Older or less fit patients may not be able to tolerate the aggressive chemotherapy regimens used in those who are fit and less than 60 years or be candidates for SCT.

A liposomal co-formulation of cytarabine and daunorubicin (Vyxeos®, previously called CPX-351) is one of the advances in chemotherapy for AML. It was designed to achieve synergistic leukemia cell killing in vitro with a five to one molar ratio of cytarabine to: daunorubicin. The liposomes are selectively taken up by bone marrow leukemia cells in xenograft models.

Gemtuzumab ozogamicin (Mylotarg®) is a biologic consisting of a monoclonal antibody against CD33 linked to calicheamicin. The antibody attaches to CD33, which is found on 90 percent of AML cells, and the antibody-drug conjugate is internalized where calicheamicin is released to bind to DNA and create double-strand breaks that result in cell death. It is an option in combination with induction chemotherapy for initial treatment of AML that has the CD33 protein. Addition of gemtuzumab ozogamicin significantly reduces the risk of relapse and improves overall survival at five years ($p = 0.01$).[8] The most benefit is seen in those with favorable cytogenetics. It can also be used by itself, either as the first treatment (especially in people who might not be healthy enough for intense chemotherapy), or if other treatments are no longer working.

Several targeted therapies have been developed for improving OS in AML with specific mutations, and all these agents are given orally once daily. Overexpression of FLT3 is common in AML; 25 percent of cases have internal tandem duplication (FLT3-ITD) and 5 percent have point mutations in tyrosine kinase domains (FLT3-TKD).[3,9] Midostaurin (Rydapt®), a multitargeted kinase inhibitor, is added for FLT3 mutation-positive disease during induction and consolidation (days 8 to 21 of each cycle). Midostaurin improves four-year OS, reduces the risk of death by 23 percent, and improves OS after SCT (for first CR).[10] Midostaurin has been studied as maintenance therapy for one year after consolidation chemotherapy or allogenic SCT but is not FDA approved for this indication.[11] The effect of midostaurin maintenance appears to be better than historical control on CR, OS, and EFS.

The clinical benefit of FLT3 inhibitors in patients with acute myeloid leukemia has been limited by rapid generation of resistance mutations, particularly in codon Asp835 (D835). Gilteritinib (Xospata®) is another FLT3 inhibitor indicated for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation. In the Phase I/II trial of this agent, 40 percent achieved a response, with 8 percent achieving CR, 21 percent CRi, and 10 percent partial remission.[12]

In some people with AML, the leukemia cells have a mutation in the isocitrate dehydrogenase (IDH1 or IDH2) gene, an enzyme of the citric acid cycle. Mutant IDH produces 2-hydroxyglutarate (2-HG), which alters DNA methylation and leads to a block in cellular differentiation. Targeted drugs called IDH inhibitors can block the production of 2-HG. The IDH inhibitors seem to work by helping the leukemia cells differentiate into more normal cells.

Ivosidenib (Tibsovo®) is an IDH1 inhibitor. It can be used to treat AML with an IDH1 mutation, either as the first treatment in the older or unfit patient or for relapsed/refractory disease. Enasidenib (Idhifa®) is an IDH2 inhibitor. It can be used to treat AML with an IDH2 mutation, for the same indications as ivosidenib. Common adverse events of the IDH inhibitors include nausea, vomiting, diarrhea, fatigue, joint pain, shortness of breath, increased levels of bilirubin, and loss of appetite. Differentiation syndrome is a serious and potentially lethal adverse event of IDH inhibitors and sometimes with other medications for AML. The most frequent manifestations are dyspnea, fever, pulmonary infiltrates, and hypoxia. Onset appears to correspond to medication-induced myeloid cell differentiation and maturation. It is treated by holding the medication and giving corticosteroids.

B-cell lymphoma two (BCL-2) overexpression in AML allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins. Venetoclax (Venclexta®) binds to BCL-2, freeing pro-apoptotic proteins that initiate apoptosis. It is used in combination with chemotherapy (decitabine, azacytidine, low-dose cytarabine) in those with newly diagnosed AML who are 75 years or older, or who are not healthy enough to tolerate aggressive chemotherapy.[5] In trials of venetoclax in combination with single-agent chemotherapy, over 60 percent achieved CR and CRi.[13,14] Common adverse events include neutropenia, anemia, diarrhea, nausea, bleeding, thrombocytopenia, and fatigue.

AML cells can also have mutations in a cell signaling pathway called hedgehog. The hedgehog pathway is crucial for the development of the embryo and fetus and is important in some adult cells, but it can be overactive in leukemia cells because of mutation. Glasdegib (Daurismo®) targets a protein in this pathway and can be used with chemotherapy in people with newly diagnosed AML who are 75 years or older, or who are not healthy enough to tolerate aggressive chemotherapy. In this group, it has been shown to help people live longer. Common adverse events include muscle and bone pain, fatigue, neutropenia, anemia, bleeding, nausea, thrombocytopenia, and stomatitis.

Conclusion

The treatment of AML has been changing rapidly with the discovery of many different gene mutations and development of therapies targeted at these mutations. The goal is to induce remission but because of high rates of relapse patients may undergo numerous lines of therapy. The targeted medications in combination with aggressive chemotherapy regimens have led to significant improvements in survival in younger patients. Survival improvements have not been as significant in those older than 60 or who are in frail health.

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Exploring Treatment Strategies to Improve Outcomes in the Management of Narcolepsy

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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

Narcolepsy is an interesting entity that gives clinicians an insight into the sleep-wake cycle. Because this disorder has significant impact on patient quality of life, it needs to be identified and treated. There are several medications which can improve daytime sleepiness and cataplexy which occur because of dysregulated sleep and lack of orexin, respectively.

Key Points

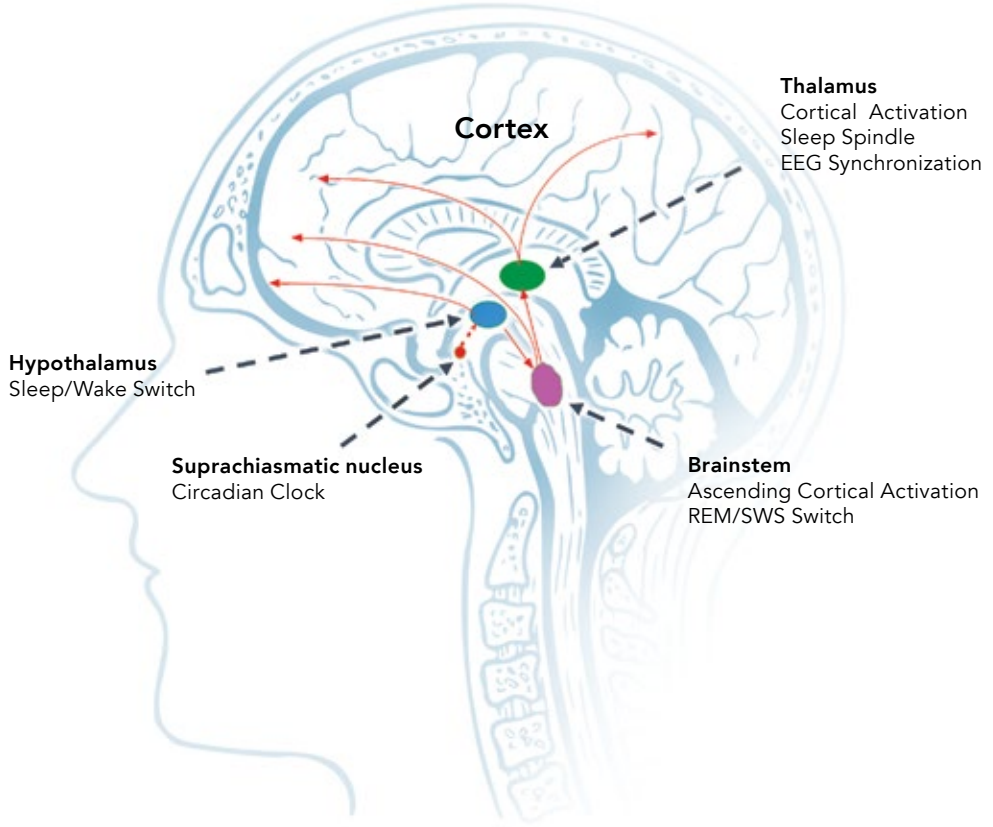
- Narcolepsy is often misdiagnosed as a different or other condition.
- The medications to treat narcolepsy decrease daytime excessive sleepiness and some improve sleep quality and decrease cataplexy.
- Acetylcholine, norepinephrine, dopamine, serotonin, histamine, and orexin are neurotransmitters targeted by medications.
- Treating comorbid disorders and nonpharmacologic sleep hygiene strategies are the first-line treatments

NARCOLEPSY IS A CHRONIC NEUROlogical disorder caused by the brain's inability to regulate sleep-wake cycles and is characterized by excessive daytime sleepiness (EDS)[1] At various times throughout the day, people with narcolepsy experience overpowering bouts of sleep. Those affected have cognitive issues such as memory issues, difficulty with executive function, and mood changes. They also have issues with workplace performance and fatigue-related accidents. In addition to EDS, people with narcolepsy can have cataplexy (the sudden loss of voluntary muscle tone), vivid hallucinations during sleep onset or upon awakening, and sleep paralysis. Approximately 25 percent of those with narcolepsy have abnormal breathing during sleep. Other co-occurring issues are periodic limb movement in sleep, restless leg syndrome, depression, and anxiety. Because narcolepsy is often misdiagnosed as other conditions, it may take years to get the proper diagnosis.

The circadian clock of the brain drives sleep-wake cycles, and light is an important determinant for this clock. Melatonin secretion after dark turns off wakefulness and the drive to stay awake rapidly diminishes. Every individual has their own circadian rhythm; some are early melatonin produces and others are late. The medications to treat narcolepsy interact with the circadian process. The suprachiasmatic nucleus (SCN) in the brain is the master circadian clock (Exhibit 1) which communicates with the thalamus, brainstem, hypothalamus, and cortex. Many neurochemically distinct systems in the brain interact to regulate wakefulness and sleep. Wakefulness is promoted by brainstem and hypothalamic neurons producing acetylcholine, norepinephrine, dopamine, serotonin, histamine, and orexin (also known as hypocretin); these neurotransmitters are targeted by the various medications for narcolepsy. Each of these arousal systems is capable of increasing wakefulness, but coordinated activity in all these pathways is required for complete alertness and cortical activation. Because orexin promotes wakefulness and inhibits rapid eye movement (REM) sleep, its absence in narcolepsy permits inappropriate transitions between wakefulness and sleep.

Narcolepsy may have several causes. Although the cause of narcolepsy is not completely understood, current research suggests that narcolepsy may be the result of a combination of factors working

Exhibit 1: Neurophysiology of Sleep



together to cause a lack of orexin.[2] These factors include autoimmune disorders, genetics, and brain injury. Nearly all people with narcolepsy who have cataplexy have extremely low levels of orexin. Orexin levels are usually normal in people who have narcolepsy without cataplexy. Although the reason for orexin producing cell loss is unknown, it appears to be linked to an autoimmune attack on the orexin-containing brain cells because of a combination of genetic and environmental factors. Most cases of narcolepsy are sporadic. However, clusters in families sometimes occur—up to 10 percent of individuals diagnosed with narcolepsy with cataplexy report having a close relative with similar symptoms. Rarely does narcolepsy result from traumatic injury to parts of the brain that regulate wakefulness and REM sleep or from tumors and other diseases in the same region.

Treating comorbid disorders and nonpharmacologic sleep hygiene strategies are the first-line treatments (Exhibit 2).[1] Improving the quality of nighttime sleep can combat EDS and help relieve persistent feelings of fatigue. Good sleep hygiene measures, such as maintaining a regular sleep schedule, relaxing before bed, and avoiding large meals, alcohol, and caffeine-containing beverages before bedtime, can enhance sleep quality.

Medications approved for EDS in narcolepsy include modafinil (Provigil®, generic), armodafinil (Nuvigil®, generic), sodium oxybate (Xyrem®) solriamfetol (Sunosi®) and pitolisant (Wakix®). Solriamfetol and pitolisant were both approved by the FDA in 2019. Amphetamine derivatives are also occasionally used, but there are concerns about tolerance, abuse, misuse, and adverse events. Cataplexy can be treated with sodium oxybate and various antidepressants which are also potent inhibitors of the REM generator in the brain but only sodium oxybate is FDA approved for managing cataplexy (Exhibit 3).

Modafinil and armodafinil, the R-isomer of modafinil, have lower potency than amphetamines, few peripheral side events, and lower addictive potential than amphetamines. Because of abuse potential, they are Schedule IV controlled substances. Their mechanism of action is debated but probably involves dopamine transmitter inhibition

Exhibit 2: General Approach to Narcolepsy Management for All Patients[1]

Comorbid Disorders	Nonpharmacological Measures

Assess and treat
• Sleep apnea
• Restless leg syndrome
• Psychiatric and neurologic disorders
	Behavioral factors
	• Sleep hygiene
	  ○ Structured nocturnal sleep and wake times
	  ○ Naps—scheduled and PRN
	• Exercise
	Environmental factors
	• Ambient temperature
	• Light therapy
	Social factors
	• Personal and family counseling
	• Support groups

and some histaminergic activity. Armodafinil has a longer half-life, which may make it more effective than modafinil. The most common adverse events of these two medications are headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia.

Sodium oxybate is the sodium salt of gamma hydroxybutyrate (GHB), a Schedule I controlled substance. Sodium oxybate is thought to act via GABA B or specific GHB receptors. It reduces dopamine release at night and likely causes secondary dopamine increase during day. Sodium oxybate is indicated for the treatment of EDS and cataplexy in patients with narcolepsy who are seven years and older. Because of the risks of CNS depression, abuse, and misuse, sodium oxybate, a Schedule III controlled substance, is available only through a restricted distribution program called the XYREM REMS Program, using a central pharmacy that is specially certified. Prescribers and patients must enroll in the program. Besides the prescribing restrictions and abuse potential, bi-nightly dosing is necessary. Half of the prescribed dose is given in the bed at bedtime and the other half 2.5 to 4 hours later (which requires the patient to set an alarm to get up and take the dose). The initial starting dose is 4.5 grams, which can be increased to 9 grams. The bedtime dose has immediate effects on disturbed nocturnal sleep; sodium oxybate is the only narcolepsy agent that has been shown to improve nighttime sleep.[3] Therapeutic effects on cataplexy and EDS are often delayed. It is contraindicated in combination with sedative hypnotics or alcohol and in those with succinic semialdehyde dehydrogenase deficiency. The most common adverse events are nausea, dizziness, vomiting, somnolence, enuresis, and tremor. It also has a black box warning that CNS depression from this agent can result in seizure, respiratory depression, decreased consciousness, coma, and death. Overall, this agent reduces EDS, increases daytime alertness, improves night sleep, and reduces the number of cataplectic attacks.

Solriamfetol is approved for EDS from narcolepsy and obstructive sleep apnea. It is a norepinephrine–dopamine reuptake inhibitor (NDRI) and is derived from phenylalanine. The dose is 75 or 150 mg taken once daily for patients with narcolepsy and it is a Schedule IV controlled substance. The mean changes from baseline were 9.8 minutes for solriamfetol 150 mg on the Maintenance of Wakefulness Test (MWT) versus 2.1 minutes for placebo, and -5.4 for 150 mg on the Epworth Sleepiness Scale (ESS) score versus -1.6 for placebo (all $p < 0.0001$).[4] At week 12, higher percentages of patients treated with solriamfetol 150 mg (78.2%) reported Patient Global Impression of Change (PGIC) improvement relative to placebo (39.7%; both $p < 0.0001$). The most common adverse events are headache, nausea,

Exhibit 3: Pharmacologic Treatment of Narcolepsy

Excessive Daytime Sleepiness	Cataplexy
• Amphetamine salts	• Sodium oxybate
• Dextroamphetamine	• SNRI: venlafaxine
• Methamphetamine	• SSRI: fluoxetine, sertraline
• Methylphenidate	• Norepinephrine reuptake inhibitor: atomoxetine
• Modafinil/Armodafinil	• Anticholinergics: tricyclics
• Pitolisant	
• Solriamfetol	
• Sodium oxybate	

decreased appetite, insomnia, and anxiety. This agent has efficacy for at least nine hours during the day and, no rebound after stopping the agent has been seen.

Pitolisant, a histamine three (H3) receptor antagonist/inverse agonist, increases histamine synthesis and release. Histaminergic neurons in the posterior hypothalamus stimulated by orexin neurons control waking, feeding, learning, and memory (H1 through H4). H3 is an auto receptor and presynaptic heteroreceptor. H3 suppresses histamine neuronal firing and inhibits synthesis and release of histamine. H3 also inhibits the release of acetylcholine, noradrenaline, and dopamine. Dosing starts with 8.9 mg once a day and can be increased to 35.6mg daily with weekly dose changes. The most common adverse events are headache, insomnia, nausea, and anxiety. Pitolisant reduced EDS comparable to modafinil and better than placebo, improved attention, decreased cataplexy frequency (40% to 76%), and increased MWT sleep latency by 80 percent.[5-7] The FDA only approved this agent for EDS, even though it has shown benefits on cataplexy and is approved in Europe for this indication. Importantly, this agent is not a controlled substance, unlike all the other agents for EDS.

Antidepressants that increase the amount of serotonin, norepinephrine, and dopamine in the brain can be used to manage cataplexy.[8] Venlafaxine, sertraline, and fluoxetine are primarily used. An issue with these is rebound in the case where the patient suddenly stops the medications.

Conclusion

Therapeutic intervention for narcolepsy should incorporate behavioral and pharmacologic therapy. The medications to treat narcolepsy decrease daytime excessive sleepiness, and some improve sleep quality and decrease cataplexy by targeting various neurotransmitters.

Recent medication approvals by the FDA have expanded treatment options to include different mechanisms of action.

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Navigating an Increasingly Complex Treatment Landscape in the Management of Hepatocellular Carcinoma (HCC)

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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 several therapies for advanced hepatocellular carcinoma (HCC) that have been shown to improve survival for this incurable stage of the disease. Oral tyrosine kinase inhibitors (TKIs), alone or in combination with immunotherapy, are the first-line therapy. Combinations are likely to become the standard of care and will hopefully continue to extend the survival benefits of treatment.

Key Points

- First-line treatment of advanced unresectable HCC is either a TKI or a combination of immunotherapy and an anti-VEGF agent.
- A combination of immunotherapy and TKI is likely to become the standard of care for first-line therapy.

HEPATOCELLULAR CARCINOMA (HCC) is the most common type of primary liver cancer and occurs most often in people with chronic liver diseases, such as cirrhosis caused by hepatitis B (HBV) or hepatitis C infection or nonalcoholic fatty liver disease (NAFLD).[1] The incidence of HCC varies considerably around the world, with the highest rates in Southeast Asia and sub-Saharan Africa (where HBV infection is endemic and high). The United States (U.S.) has intermediate incidence areas, with age-adjusted incidence rates close to 4 per 100,000 person-years).[2]

Treatment options for HCC depend on the size, number, and location of tumors; presence or absence of cirrhosis; whether the cirrhosis is compensated or decompensated; operative risk based on the extent of cirrhosis and comorbid diseases; overall performance status; portal vein patency; and presence or absence of metastatic disease. The American Association for the Study of Liver Diseases (AASLD) has published guidelines for treating HCC, but they have not been updated since 2018 and thus do not include data from recently published or presented trials.[3] The National Comprehensive Cancer Network (NCCN) guidelines are the most up to date, having been updated in May 2020.[4]

The major recent changes in HCC treatment have occurred in the recommendations for advanced unresectable disease. Advanced unresectable disease has been treated with tyrosine kinase inhibitors (TKIs) since the approval of sorafenib in 2007. Lenvatinib, a second- generation TKI, was found to be non-inferior to sorafenib for overall survival (OS) at 13.6 (12.1 to14.9) months versus 12.3 (10.4 to 13.9) months.[5] Lenvatinib was better for secondary endpoints of improved time to progression (8.9 versus 3.7 months), objective response rate (ORR, 24.1% versus 9.2%), and progression-free survival (PFS, 7.3 versus 3.6 months). Lenvatinib was approved in 2018 for first-line treatment of unresectable HCC. Adverse event rates are similar between lenvatinib and sorafenib. Diarrhea, fatigue, weight loss, and anorexia are some of the most common adverse events of both agents. Hypertension is more common with lenvatinib, and palmar-plantar erythrodysesthesia is more common with sorafenib. Although sorafenib had been the standard of care for first-line treatment of advanced HCC for more than

Exhibit 1: Summary of Agents Beyond First Line[6-9]

	Regorafenib versus PBO	Cabozantinib versus PBO	Ramucirumab versus PBO (AFP > 400)	Pembrolizumab versus PBO
mOS	HR = 0.63	HR = 0.76	HR = 0.73	HR = 0.781
mPFS	HR = 0.46	HR = 0.44	HR = 0.452	HR = 0.718
ORR	10.6 versus 4.1%	4.0 versus 0.4%	4.6 versus 1.1%	17.0 versus 4.4%
G3/4T	PPE, HTN	PPE, HTN	HTN	irAE

HR = hazard ratio; PBO = placebo; mOS = median overall survival; mPFS = median progression-free surivival;

ORR = objective response rate; G3/4T = Grade 3 or 4 toxicity; PPE = palmar-plantar erythrodysesthesia;

HTN = hypertension; irAE = immune-related adverse events

a decade, once lenvatinib became available, many clinicians switched to it and is now a preferred agent with a Category 1 recommendation in the NCCN guidelines.[4]

There are several other TKIs that are currently only approved for use as second-line therapy (Exhibit 1).[6-9] Regorafenib was approved in 2017 by the FDA for use in patients with HCC who have been previously treated with sorafenib. Ramucirumab is a VEGF receptor 2 antagonist that was FDA approved in 2019 as monotherapy for HCC in patients with alpha-fetoprotein (AFP) of 400 ng/mL or higher who have been previously treated with sorafenib. Cabozantinib was approved in 2019 for HCC in patients previously treated with sorafenib. Each of these provide some improvement in OS and PFS compared to placebo in the second-line setting. The adverse event profile of these second-line TKIs is like that seen with sorafenib and lenvatinib.

As with many other cancers, checkpoint inhibitor immunotherapy is now a treatment option for HCC. Pembrolizumab was FDA approved in 2018 for patients with HCC previously treated with sorafenib. Approval was based on the KEYNOTE-224 trial, in which single-agent pembrolizumab produced an ORR of 17 percent among 104 patients.[9] The complete response (CR) rate was 1 percent, partial response (PR) was 16 percent, stable disease (SD) was 44 percent, and 33 percent had progressive disease (PD). The median time to response was 2.1 months and duration of response greater than or equal to nine months occurred in 77 percent. In the Phase III trial of pembrolizumab in this same setting (Keynote-240), OS and PFS did not reach statistical significance per specified criteria [median OS: 13.9 versus 10.6 months (p = .0238), median PFS: 3.0 versus 2.8 months (p = .0022)].[10]

Nivolumab monotherapy was approved in 2017 for HCC under an accelerated approval based on the CheckMate 040 trial which showed an ORR of 20 percent (18% PR, 45% SD), median OS of 13.2 months (8.6 - ∞), and PFS of 4.0 months (2.9 to 5.4).[11] Data from the CheckMate 459 Phase III trial comparing nivolumab to sorafenib in first-line treatment of advanced HCC patients were presented at the 2019 European Society for Medical Oncology (ESMO) Congress. OS did not meet the predefined threshold of statistical significance (hazard ratio [HR] 0.84, p = 0.0419). Median OS was 16.4 months for nivolumab and 14.7 months for sorafenib (HR 0.85 [95% CI: 0.72 to 1.02]; p = 0.0752).[12] Clinical benefit was observed across predefined subgroups, including hepatitis infection status, presence of vascular invasion and/or extrahepatic spread, and region (Asia versus non-Asia). ORR was 15 percent for nivolumab (14 patients with CR) and 7 percent for sorafenib (5 patients with CR). Grade 3/4 treatment-related adverse events were reported in 22 percent in the nivolumab arm and 49 percent in the sorafenib arm and led to discontinuation in 4 percent and 8 percent of patients, respectively.

Some clinicians have speculated on why the Phase III trials with immune checkpoint therapy have been negative so far. Statistical issues including the use of co-primary endpoints, ambitious hazard ratios, and inadequate power may explain the results. It may also be an issue of measuring median OS versus tail of the curve survival (i.e., the small percentage of patients who achieve long-term survival and possibly cure with immunotherapy). Proving differences in median OS is a challenge in the age of multiple therapeutic options and cross-over. Other considerations are whether the activity of immunotherapy alone is sufficient. Biomarkers

Exhibit 2: Ongoing Phase III Studies of Checkpoint Inhibitors in Advanced HCC

Study Identifier	Target Accrual	Eligibility	Randomization
LEAP-002 (NCT03713593)	750	First-line, advanced HCC	• Lenvatinib + Pembrolizumab • Lenvatinib
IMbrave150 (NCT03434379)	480	First-line, locally advanced or advanced HCC	• Atezolizumab + Bevacizumab • Sorafenib
HIMALAYA (NCT03298451)	1,310	First-line advanced HCC	• Durvalumab • Durvalumab + Tremelimumab (2 regimens) • Sorafenib
COSMIC-312 (NCT03755791)	640 (6:3:1)	First-line, advanced HCC	• Cabozantinib + Atezolizumab • Sorafenib • Cabozantinib

for response of HCC to immunotherapy are needed.

With several treatment options for second-line therapy, clinicians must weigh how to choose a therapy. The NCCN guidelines list numerous options for second and beyond lines of therapy.[4] Regorafenib, cabozantinib, and ramucirumab AFP > 400 ng/mL have Category 1 recommendations because there is Level 1 evidence showing survival benefits for each. Lenvatinib, sorafenib, nivolumab, nivolumab/ipilimumab, and pembrolizumab (Category 2B, others Category 2A) are also options but have less data to support their use. There is no Level 1 evidence showing survival benefit for the use of immunotherapy options for any line of therapy. Safety profiles, tumor burden, aggressiveness of the tumor, and patient preferences are all considerations in selecting second-line and beyond therapy.

Combination therapy of immunotherapy and TKI is one way to continue to improve survival with advanced HCC. Recently published data support the combination of atezolizumab, an anti-programmed cell death ligand 1 (PD-L1) antibody, plus bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), for first-line treatment of advanced HCC. The Phase III IMbrave 150 trial randomly assigned 501 previously untreated patients with advanced unresectable HCC two to one to atezolizumab plus bevacizumab or sorafenib. Preliminary data from the trial were reported at the 2019 ESMO Asia Congress. There were significant improvements in median OS and PFS. Six-month OS was 85 percent with the combination compared to 72 percent with sorafenib; median OS was not reached compared to 13.2 months, respectively.[13] Median PFS was 6.8 months versus 4.5 months with sorafenib (HR 0.59, 95% CI, 0.47 to 0.76; $p < 0.0001$), and the overall response rate was 27 percent versus 12 percent ($p < 0.0001$). The NCCN guidelines were updated in March 2020 to include this combination as a preferred first-line option for advanced HCC along with sorafenib and lenvatinib, and FDA approval is likely to occur in 2020. Exhibit 3 summarizes the currently preferred sequencing of therapies.

Breakthrough therapy designation was granted by the FDA in July 2019 to pembrolizumab in combination with lenvatinib for the potential first-line treatment of patients with advanced unresectable HCC not amenable to local-regional treatment. The designation is based on updated interim results from the KEYNOTE-524 trial. The ORR was 36.7 percent, consisting of 1 CR and 10 PR.[14] A Phase III trial of first-line pembrolizumab plus lenvatinib plus versus lenvatinib plus placebo in advanced HCC is ongoing. This combination has not yet been FDA approved for advanced HCC nor is it included yet in the NCCN guidelines. Many more combinations of immunotherapy and TKI are currently under study (Exhibit 2) and likely will be approved as first-line treatment in the coming years.

Exhibit 3: How to Best Sequence Patients with Advanced Disease

First-Line	Second-Line	Third-Line
Sorafenib	Regorafenib	Cabozantinib
Lenvatinib	Cabozantinib	Nivolumab or Pembrolizumab
Atezolizumab/bevacizumab	AFP > 400: Ramucirumab	
Clinical Trials		

Conclusion

First-line treatment of advanced unresectable HCC is either a TKI or a combination of immunotherapy and an anti-VEGF agent. Combination of immunotherapy and TKI is likely to become the standard of care for first-line therapy. There are also numerous choices for second-line and beyond therapy.

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The Importance of Early Diagnosis in the Treatment and Management of Epilepsy

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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

Treating epilepsy requires an accurate and timely diagnosis and then selecting the least toxic and most likely effective medications. Several antiepileptic drugs (AEDs) have been approved in recent years; however, even with these advances, 35 percent or more of patients have uncontrolled seizures. Surgical therapies may be an option for these patients.

Key Points

- Early diagnosis of epilepsy is critical for reducing negative outcomes.
- Sixty to 70 percent of patients with epilepsy will respond to AED therapy.
- The risk of adverse events compared to the benefits of seizure control must be considered when choosing therapy.
- Resective surgery offers the potential for cure.

EPILEPSY IS A DISEASE CHARACTERIZED by recurrent, unprovoked seizures, which are paroxysmal, self-limited alterations of behavior produced by abnormal, excessive, synchronous firing of populations of neurons. One in 26 persons will develop epilepsy in their lifetime with a cumulative incidence of 3.8 percent. More than 300,000 people have a first seizure each year and 150,000 new cases of epilepsy are diagnosed yearly. The highest incidence is in those less than two years of age and greater than 65 years old. Over two million people have active epilepsy in the United States U.S.), with 570,000 of these individuals over the age of 65. Unfortunately, 35 to 40 percent of patients with epilepsy are considered refractory to medical therapy.

When diagnosing epilepsy, it is important to distinguish the various types of seizures. Provoked seizures are those that occur in the context of an acute metabolic disturbance, or at the time of an acute insult to the central nervous system. Patients can also have a single unprovoked seizure and not have epilepsy, but a single unprovoked seizure is included in the definition of epilepsy. One unprovoked seizure and a probability of further seizures like the general recurrence risk after two unprovoked seizures is included in the definition. There are also seizure mimics which need to be ruled out. These include syncope, movement disorders, and psychogenic nonepileptic seizures.

Exhibit 1 shows the current classification of various seizure types.[1] 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.[2] Provoking causes are ruled out with standard metabolic testing, liver and renal function tests, urinalysis, toxicology screens, and CT scan or MRI. Electroencephalogram (EEG), lumbar puncture, and further endocrine studies may also be needed.

Early diagnosis is critical for reducing negative outcomes. Untreated infantile spasms are associated with permanent intellectual disability and increased mortality. Untreated absence seizures are often associated with poor school performance. Injury resulting from car accidents, burns, and falls also occur with uncontrolled seizure. Mortality occurs through injuries, drownings, and sudden unexpected death in epileptic persons (SUDEP).

Exhibit 1: Classification of Seizure Types[1]

Focal Onset		Generalized Onset	Unknown Onset
Aware	**Impaired Awareness**	**Motor**	**Motor**
Motor Onset		tonic-clonic	tonic-clonic
automatisms		clonic	epileptic spasms
atonic		tonic-clonic	**Non-Motor**
clonic		myoclonic	behavior arrest
epileptic spasms		myoclonic-tonic-clonic	
hyperkinetic		myoclonic-atonic	**Unclassified**
myoclonic		atonic	
tonic		epileptic spasms	
Non-Motor Onset		**Non-Motor (absence)**	
autonomic		typical	
behavior arrest		atypical	
cognitive		myoclonic	
emotional		eyelid myoclonia	
sensory			
Focal to bilateral tonic-clonic			

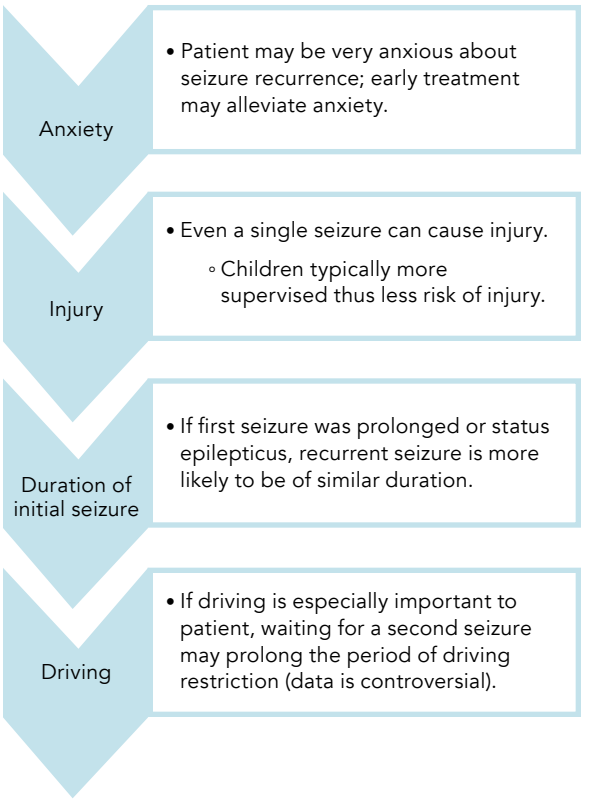
SUDEP excludes death due to drowning, status epilepticus, or toxicologic or anatomical cause. Overall, in epilepsy, the risk of SUDEP is 1 per 1,000 person-years and in drug-resistant epilepsy it is 1 per 100 person-years.[3] The risk is higher in the setting of generalized tonic-clonic seizures.

After a single unprovoked seizure, clinicians, in consultation with the patient, must decide whether to pursue treatment. Antiepileptic drugs (AEDs) in patients presenting with a first tonic-clonic seizure reduce the risk of relapse; however, 50 percent of patients who are not treated will never experience a second seizure. The FIRST trial showed that treating a first unprovoked seizure did not improve prognosis.[4] Patients treated after the first seizure and those treated after seizure relapse had the same time-dependent probability of achieving one and two seizure-free years. None of the variables that were prognostic predictors of relapse was significantly associated with the probability of having one or two years of seizure control. Moreover, the probability of long-term remission is not influenced by treatment of the first seizure.

The MESS trial found that immediate treatment of a first unprovoked seizure increased the time to first recurrence, second recurrence and first generalized tonic-clonic seizure. Immediate treatment reduced the time to achieve two-year remission, but this effect was lost after two years.[5] Adverse events were 8 percent higher in the immediate treatment versus the deferred treatment group.

The American Academy of Neurology (AAN) has published an evidence-based guideline on managing first seizures.[6] Whether to initiate immediate AED treatment after a first seizure should be based on individualized assessments that weigh the risk of recurrence against the adverse events of AED therapy, patient preferences, and advise that immediate

Exhibit 2: Other Treatment Considerations



treatment will not improve the long-term prognosis for seizure remission but will reduce seizure risk over the next two years.[5] Clinical variables associated with increased risk of a second seizure include a prior brain insult, an EEG with epileptiform abnormalities, a significant brain-imaging abnormality, and a nocturnal seizure. Other treatment considerations in deciding whether to treat a first unprovoked seizure are shown in Exhibit 2.

Treatment modalities for epilepsy include pharmacologic (AED), surgical (resective, transactive, implanted neurostimulation), dietary, and alternative agents. AEDs are the first line of treatment, and the goal of treatment with AEDs is for the patient to be seizure free with tolerable adverse events. Unfortunately, only 47 percent of people will be seizure free on the first medication tried, and 36 percent will not be seizure free even when tried on all available agents (Exhibit 3).[7]

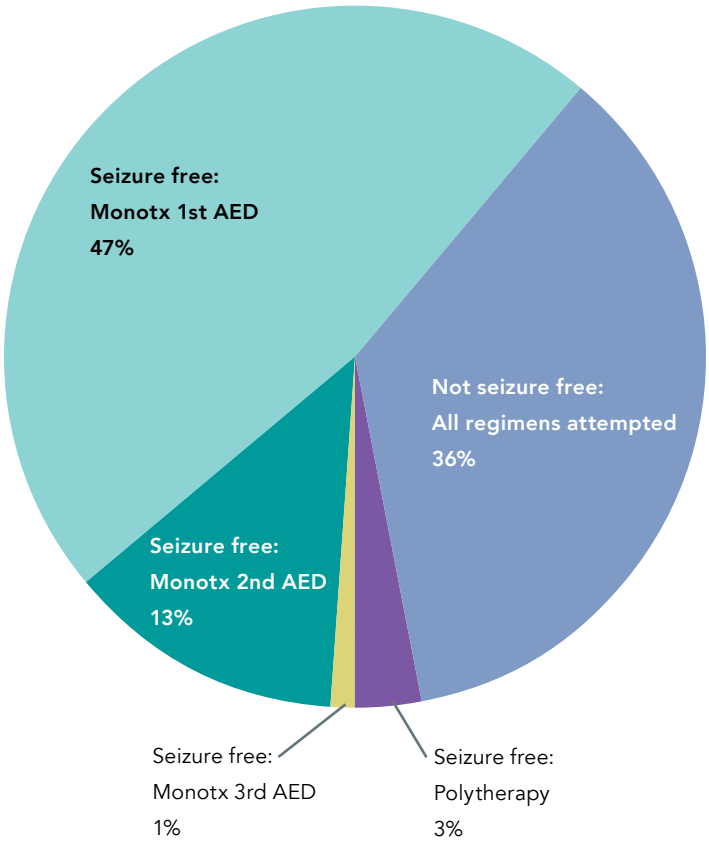
Medications should be chosen based on the seizure type. Exhibit 4 shows the typically recommended first-line therapies for various seizure types.[8] First-line therapies are either more effective or less toxic than the second-line agents. In selecting therapy, clinicians need to consider age- and gender-specific concerns regarding organ toxicities and drug interactions, neurobehavioral and cognitive concerns, comorbidities, and concomitant medications. Typically, the dose of an AED needs to be slowly titrated upward to minimize adverse events. All patients should have a monitoring plan for AED effectiveness and tolerability.

Several AEDs have been FDA approved in recent years which have unique mechanism of actions or unusual adverse events. Vigabatrin (Sabril®) irreversibly inhibits gamma-aminobutyric acid (GABA) transaminase, thus increasing GABA concentration at the synapse. This agent is not for first-line use because it can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, it may also decrease visual acuity, and the risk increases with increasing dose and cumulative exposure. It is FDA approved for refractory complex partial seizures as adjunctive therapy in patients two years of age and older who have responded inadequately to several alternative treatments and for monotherapy in infants one month to two years of age with infantile spasms for whom the potential benefits outweigh the potential risk of vision loss.

Perampanel (Fycompa®) is a non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on postsynaptic neurons. It is FDA approved for patients with epilepsy aged four years and older for partial-onset seizures with or without secondarily generalized seizures, and as adjunctive therapy for patients aged 12 years and older for primary generalized tonic-clonic seizures. This agent has a black box warning about serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats. These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression.

Two agents have been approved for seizures associated with Lennox-Gastaut syndrome (LGS), complex, rare, and severe childhood-onset epilepsy. It is characterized by multiple and concurrent seizure types, cognitive dysfunction, and slow spike waves on electroencephalogram (EEG). Clobazam (Onfi®) is a benzodiazepine approved in the U.S. for adjunctive treatment of seizures in LGS. Cannabidiol (Epidiolex®) was approved in 2019 for the treatment of LGS and Dravet syndrome (DS). DS, previously known as severe myoclonic epilepsy of infancy, is an autosomal dominant genetic disorder which causes a catastrophic form of epilepsy, with prolonged seizures that are often triggered by hot temperatures

Exhibit 3: Efficacy of Anti-Seizure Medications[7]



Monotx = monotherapy; AED = antiepileptic drug

or fever. Cannabidiol (CBD) reduced convulsive seizures in DS and dropped seizures in LGS by 17 percent to 23 percent compared with placebo as add-on therapy in patients two years of age and older.[9] Data from 25 U.S.-based sites using CBD through an expanded access program found that add-on CBD reduced median monthly convulsive seizures by 51 percent and total seizures by 48 percent at 12 weeks of treatment; reductions remained similar through 96 weeks.[10] The proportion of patients with ≥ 50 percent, ≥ 75 percent, and 100 percent reductions in convulsive seizures were 52 percent, 31 percent, and 11 percent, respectively, at 12 weeks, with similar rates through 96 weeks. CBD was generally well tolerated; the most common adverse events were diarrhea (29%) and somnolence (22%).

Midazolam nasal spray (Nayzilam®) and diazepam nasal spray (Valtoco®) were FDA approved in 2019 and 2020, respectively, for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 12 years of age and older and six years and older, respectively. These medications are intended to be used as an at home rescue medication to interrupt the seizure activity, and they do not replace maintenance AEDs. This is an important education point for patients and their caregivers to understand, along with training on how to administer the spray. Midazolam is given as a single 5 mg dose into one nostril; a second dose into the opposite nostril may be administered after 10 minutes if the patient has not responded to the initial dose. It is recommended that this agent be used to treat no more than one episode every three days and no more than five times per month. Diazepam is dosed-based on age and weight so may require sprays into each nostril for the initial dose and the interval for giving a second dose is four hours. Diazepam should be used to treat no more than one episode every five days and no more than five episodes per month.

Adherence with maintenance AEDs is a challenge in epilepsy management. One strategy to improve

Exhibit 4: Medication Selection[8]

	Tonic-Clonic	Focal*	Absence	Atypical Absence, Myoclonic, Atonic
First-line	Valproic acid	Carbamazepine	Valproic acid	Valproic acid
	Lamotrigine†	Oxcarbazepine	Ethosuximide	
	Levetiracetam†	Phenytoin		
		Lamotrigine		
		Valproic acid		
Alternatives	Topiramate	Topiramate	Lamotrigine†	Lamotrigine†
	Zonisamide†	Levetiracetam†	Clonazepam	Topiramate
	Felbamate†	Tiagabine†		Clonazepam
	Primidone	Zonisamide†		Felbamate†
	Phenobarbital	Gabapentin†		Rufinamide†
	Perampanel†	Pregabalin†		Levetiracetam†
		Primidone		
		Phenobarbital		
		Eslicarbazepine†		
		Felbamate†		
		Lacosamide†		
		Perampanel†		
		Vigabatrin†		
		Brivaracetam		

*Includes focal seizures with or without loss of awareness and focal seizures evolving to bilateral, convulsive seizures

†Approved by FDA as adjunctive therapy.

adherence includes allowing the patient enough time to come to terms with the diagnosis, results of investigations, treatment, and prognosis. Another is to choose treatment with a specific focus on matching the adverse event profile to the patient's lifestyle and clinical history. It is also important to involve family members in the management plan and to provide a medication box for patients known to have difficulty with adherence. Cell phone alarms can be extremely useful in helping patients remember to take medication on time. Plasma levels when possible are useful for ensuring adherence. At each visit, clinicians should ask specifically about individual adverse events, such as dizziness, sedation, depression, libido, and weight gain to assess their impact on adherence. Clinicians can also consider discussing SUDEP with the patient to impress upon them the reason seizure control is important.

For patients with selected types of seizures, resective surgery offers the possibility of cure by removing the epileptogenic zone within the brain. Resective surgery for treatment of epilepsy significantly reduces seizures, most strikingly after medial temporal resection (77% one-year remission) compared to neocortical resection (56% one-year remission).[11] Resective epilepsy surgery has a gradual but lasting

effect on quality of life (QOL), but minimal effects on anxiety and depression. Longer follow-up will be essential to determine ultimate seizure remission, QOL, and psychiatric outcomes of epilepsy surgery.

Neurostimulation is also an adjunctive therapy for difficult to control seizures. It includes implantable vagal nerve stimulation (VNS) or responsive neurostimulation (RNS). Indications for VNS therapy include focal, multifocal epilepsy, drop attacks (tonic/atonic seizures), Lennox-Gastaut syndrome, tuberous sclerosis complex-related multifocal epilepsy, and unsuccessful resective surgery.[12] Early complications of VNS include intraoperative bradycardia and asystole during lead impedance testing, peratracheal hematoma, infections (3% to 8%), and vagus nerve injury followed by hoarseness, dyspnea, and dysphagia because of vocal cord paralysis. Delayed morbidity due to the device includes late infections or problems in wound healing; other rarer events are due to late injury of the vagus nerve.

Neuropace® RNS is an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than two epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and /or secondarily generalized seizures). Seizures were significantly reduced by this treatment (-37.9%, n = 97) compared to a sham treatment group (-17.3%, n = 94; p = 0.012).[13] Implantation of the device is associated with risks which can include infection, intracranial hemorrhage, tissue damage, temporary pain at the implant site, cerebrospinal fluid leakage, seroma, and paralysis.

A ketogenic diet is often remarkably effective in patients who have failed numerous drug trials. The classic ketogenic diet provides 3 to 4 grams of fat for every 1 gram of carbohydrate and protein. The ketogenic diet has been shown in many studies to be particularly helpful for some epilepsy conditions. These include infantile spasms, Rett syndrome, tuberous sclerosis complex, Doose syndrome, DS and, glucose transporter type 1 deficiency syndrome (GLUT-1).[14] A formula-only ketogenic diet for infants and gastrostomy-tube fed children may lead to better compliance and possibly even improved efficacy. Although effective in children, a ketogenic diet is unrealistic for many adult patients because of the limited food choices. Hypercholesterolemia, constipation, acidosis, anorexia, dehydration, diarrhea, hypoglycemia, and renal stones are some of the potential adverse events of this diet.

Conclusion

Early diagnosis and treatment of epilepsy is critical toward improving outcomes and reducing mortality. Sixty to 70 percent of patients with epilepsy will respond to AED therapy. The risk of adverse events compared to the benefits of seizure control must be considered when selecting AEDs. For those not controlled on medications, resective surgery offers the potential for cure. Other therapies for uncontrolled seizures include VNS, RNS, and a ketogenic diet.

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Recent Treatment Advances in Inflammatory Bowel Disease: Greater Outcomes through Personalized Approaches

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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

Inflammatory bowel disease is really two separate diseases – ulcerative colitis and Crohn's disease. Optimized treatment requires a personalized approach, which considers disease factors such as subtype and severity and patient-related factors to select the best therapy. The goal of treatment is to achieve no or minimal disease activity.

Key Points

- Ulcerative colitis and Crohn's disease may require different treatments.
- Medication selection should be based on patient factors, disease subtype, severity, and the medication mechanism of action.
- A stepped approach to therapy should not be used.
- Failure of older therapies should not be a requirement for biologic use.

INFLAMMATORY BOWEL DISEASE (IBD) includes ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis. It is an autoimmune disease that appears to result from a genetic predisposition triggered by some environmental issue, which appears to be a change in the gut microbiome. IBD is a global disease with increasing incidence in newly industrialized countries that are becoming more westernized. An estimated 3.1 million adults in the United States (U.S) have IBD (1.3% of the U.S. population). The prevalence is 286 per 100,000 people in the U.S.[1] The prevalence has been rising among Hispanics and non-Hispanic whites.

UC was first described by Samuel Wilks in the 1800s. It is a continuous colonic mucosal inflammation, extending proximally from the rectum. The natural history is to have periods of remission and flares. The typical age of onset is between 15 and 40; however, there is a second peak between 50 and 80.[2] Symptoms of UC include bloody diarrhea, bowel urgency, tenesmus, and abdominal pain. It is rare to have weight loss or fevers with UC. Extraintestinal manifestations include peripheral arthropathy, ankylosing spondylitis, erythema nodosum, pyoderma gangrenosum, primary sclerosing cholangitis, uveitis, scleritis, and optic neuritis. Diagnosis is based on symptoms and evidence on colonoscopy of inflammation that starts in rectum and progresses continuously. There can be erythema, granularity, friability, erosions, and/or ulcers. Currently available serologic tests lack adequate positive or negative predictive value for diagnosis or prognosis in UC. Approximately 15 percent of patients will require hospitalization for UC, and 10 percent of patients initially present with severe UC. Management is primarily pharmacologic, but surgery is also an option.

Pharmacologic treatment includes corticosteroids, mesalamine (oral or rectal), thiopurines (e.g., azathioprine/mercaptopurine – oral), anti-tumor necrosis factor (TNF) monoclonal antibodies (e.g., infliximab/adalimumab/golimumab), anti-integrin

monoclonal antibodies (vedolizumab), Janus Kinase (JAK) inhibitor (tofacitinib), and interleukin (IL) 12/23 inhibitor (ustekinumab). Surgical treatments include ileal pouch–anal anastomosis and total abdominal proctocolectomy with permanent ileostomy.

CD was first described by Dr. Burrill B. Crohn in 1932. With CD, inflammation can involve any aspect of the gastrointestinal tract, from the mouth to the anus. Classically, the disease has skip lesions (diseased areas separated by intervening normal mucosa). Like UC, the natural history includes periods of remission and flares. Typical age of onset is between 20 and 30, but there is also a second peak around age 50. The colon and the small bowel are involved in 50 percent of cases.[2] There is only small bowel involvement in 30 percent of cases and only colonic involvement in 20 percent. Twenty-five percent of patients also have perianal involvement. There are multiple different disease phenotypes with CD including inflammatory only, stricturing, penetrating (fistula formation), and combination stricturing and penetrating. With perianal disease, patients can develop abscesses, fistulas, fissures, and skin tags. The symptoms of CD vary based on disease phenotype and location of disease. Inflammatory disease produces abdominal pain, diarrhea, weight loss, and fatigue. Stricturing disease can cause lack of bowel movements, lack of flatus, abdominal pain, nausea, and vomiting. Abscess, fevers, and fistulas to other organs can occur with penetrating disease. Extraintestinal manifestations of CD occur in up to 25 percent of patients, and they are the same as those that occur with UC.

Diagnosis of CD requires typical symptoms with evidence on colonoscopy or radiology. Colonoscopy findings include patchy inflammation, erythema, granularity, friability, erosions, and/or ulcers, perianal disease, and terminal ileum involvement. CT scan and magnetic resonance enterography (MRE) are radiologic tools for diagnosis. MRE is fast becoming the first-line radiological investigation to evaluate the small bowel in patients with CD. Other testing options include capsule endoscopy and small bowel follow through. Pathology of a biopsy is confirmatory of the diagnosis rather than diagnostic. The presence of granulomas is only seen in 25 percent of cases.[2] Currently available serologic tests lack adequate positive or negative predictive value.

As with UC, management of CD includes medications and surgery. Pharmacologic options include antibiotics for abscess management; these often require drainage, if antibiotics fail. Short-term corticosteroids may be used for remission induction, but they should not be used for maintenance of remission. Mesalamine (oral or rectal) is not FDA approved for CD, but it is used in colonic disease in some cases. Immune system modulators including thiopurines (azathioprine/mercaptopurine), methotrexate, JAK inhibitor, and biologics are also options. The biologics that are FDA approved for CD include infliximab, adalimumab, certolizumab pegol, vedolizumab, and ustekinumab. Exhibit 1 summaries the various agents for both UC and CD. Surgical treatments for CD include localized resection, total proctocolectomy with permanent ileostomy, diverting ileostomy, stricturoplasty, and fistulotomy. Eighty percent of patients will eventually require surgery after 20 years of disease activity.[2]

The current treatment paradigm for IBD is to treat based on disease subtype and disease severity. Clinicians should discuss the risks and benefits of the various options, the mode of delivery (oral, rectal, subcutaneous injection, and infusion) and the attendant issues such as having to use an infusion center, and the costs of treatment. A challenge to controlling IBD in a timely manner has been that many insurance companies still require stepwise therapy failure before patients can move on to the most effective therapy, a biologic.[3] There is a move on a national level and on many state levels to prohibit step therapy requirements. The classic treatment strategy with IBD was to use a pyramid approach of starting with salicylates, like mesalamine, and corticosteroids, such as budesonide, and then move on to more aggressive therapies such as the thiopurines and methotrexate before resorting to biologics. The new paradigm is to use the appropriate medication based on disease characteristics and patient-specific factors.[4] For example, patients with mild disease may be managed with just mesalamine, whereas someone with severe disease should be treated with a biologic from the beginning. Additionally, UC and CD are not the same disease; therefore, one medication might not work for both.[5] Exhibit 2 presents safety and efficacy considerations for selecting therapy.

There are numerous guidelines on managing IBD. The American Gastroenterology Association (AGA) and the American College of Gastroenterology (ACG) have each published guidelines on managing CD and UC, and these guidelines mirror the new treatment paradigm.[6-11]

Early diagnosis and treatment are important to prevent complications such as strictures, abscess, fistulas, and especially the need for surgery. Early diagnosis for UC is common as the typical presenting symptom is bloody diarrhea. Unfortunately, early diagnosis for CD is uncommon as presenting symptoms are often nonspecific. Prior authorizations and stepwise therapy requirements can result in

Exhibit 1: Medications for IBD

Agent	Use	Route	Advantages	Disadvantages	Comments
Corticosteroids	Induction of remission UC and CD only.	IV, oral prednisone, oral budesonide (minimally absorbed), rectal foam, rectal enema.	• Most efficacious drug for induction of remission (especially in UC). • Fast response.	• Adverse events: weight gain, HTN, cataracts, glaucoma, diabetes, osteoporosis, skin changes, irritability, insomnia. • Need to plan on steroid sparing agent.	• No role in maintenance of remission Budesonide oral and rectal are not • Budesonide oral and rectal are not associated with typical steroid side events but are less efficacious than prednisone. • No role for budesonide (Uceris7/Entocort7) or other topical steroid in severe disease.
Mesalamine	Induction of remission and maintenance of remission for mild-moderate UC.	Oral or rectal	• Can be dosed once daily. Extremely safe. • No risk of antibodies. • Generic formulations available.	• Only efficacious for mild-moderate ulcerative colitis. • Once one formulation fails little benefit to trying different formulation.	• Occasionally used in colonic CD but not FDA approved for this. • Frequently used in mild CD but evidence to support this is very poor and it is not recommended. • Lab testing—yearly creatinine.
Thiopurines (Azathioprine/ Mercaptopurine)	Maintenance of remission for UD and CD.	Oral or rectal	• Oral • No antibodies • Can be combined with biologics	• Can take 3 months to reach efficacy • Adverse events: nausea, vomiting, abdominal pain, pancreatitis, bone marrow suppression, infection, hepatitis, lymphoma, non-melanoma skin cancer, cervical dysplasia. • Adverse events and lymphoma risk increases with age > 60. • No role in induction of remission. • Overall efficacy appears inferior to all biologics and more side events.	• If failed one thiopurine use of a second likely will fail too (except nausea might be responsive to switch) • Lab testing - requires TPMT checking prior to starting (if low enzymatic activity likely contraindicated); • CBC and LFTs periodically
Methotrexate	Induction of remission and maintenance of remission with CD.	Oral or subcutaneous but more effective as subcutaneous	• Can be oral • No antibodies • Can be combined with biologics.	• Can take weeks to reach efficacious levels. • Adverse events: nausea, vomiting, abdominal pain, bone marrow suppression, infection, hepatitis, cirrhosis, lymphoma. • Overall efficacy appears inferior to biologics. • Teratogenic in pregnancy. • Must take folic acid along with.	• Caution regarding pregnancy while on MTX and importance of birth control. • Lab testing; CBC and LFTs periodically.
Anti-TNF (Infliximab, Adalimumab, Golimumab, Certolizumab-Pegol)	Induction of remission and maintenance of remission for UC and CD.	Infusion (infliximab) or Self-injection	• Very efficacious class • Rapid onset of action • For infliximab—Can be used for rescue therapy in those failing steroids.	• Adverse events: infusion/ injection site reactions, infection, melanoma skin cancer, possible lymphoma risk, reactivation of TB or hepatitis B, psoriasis, eczema, drug induced lupus. • Risk of developing antibodies and loss of efficacy.	• Upcoming AGA will guidelines recommend infliximab over other agents given improved efficacy compared to subcutaneous options • Lab testing: requires TB testing and Hepatitis B testing prior to starting; CBC and LFTs periodically.

Agent	Use	Route	Advantages	Disadvantages	Comments
Anti-integrin (Vedolizumab)	Induction of remission and maintenance of remission for UC and CD.	Infusion (subcutaneous being developed)	• Efficacious agent especially in setting of moderate disease activity. • Gut selective with fewest systemic side events	• Adverse events: infection, infusion reactions, joint pains. • Risk of developing antibodies and loss of efficacy. • Not the fastest acting. • Not as efficacious in fistulizing or severe CD.	• Report of PML but unclear if it has a causative relationship. • Lab testing -consider monitoring CBC.
Anti-IL 12/23 (Ustekinumab)	Induction of remission and maintenance of remission for CD and UC.	Single infusion followed by self-injection	• Efficacious agent —might be close to on par with anti-TNF. • Rapid onset of action.	• Adverse events: infusion/ injection site reactions, infection, possible reactivation of TB, psoriasis, • Risk of developing antibodies and loss of efficacy.	• Lab testing: requires TB testing prior to starting; CBC and LFTs periodically. • Prior authorization can be challenging as often requires two separate authorizations, one for infusion dose and one for subcutaneous injections.
Janus Kinase Inhibitor (Tofacitinib)	Induction of remission and maintenance of remission for UC.	Oral pill BID	• Efficacious agent on par with anti-TNF. • Rapid onset of action. • No risk of antibodies.	• Adverse events: infection, possible reactivation of TB, Herpes Zoster, bowel perforation, pulmonary emboli, sudden death, elevated lipid panel, neutropenia, hepatitis, skin cancer, lymphoma.	• Lab testing: requires TB testing and hepatitis B (and possibly hepatitis C) prior to starting; CBC with differential and LFTs periodically. • Recent reports of pulmonary emboli and sudden death at the 10mg bid dose for prolonged periods. FDA now limits its use to post anti-TNF failure. • Dose at 5 mg BID

AGA = American Gastroenterology Association; BID = twice a day; CBC = complete blood count; L = interleukin; LFTs = liver function tests; PML = progressive multifocal leukoencephalopathy; TB = tuberculosis; TPMT = thiopurine methyltransferase.

delays in initiation of effective therapy by days to months. Comorbidities may preclude certain drug choices and prior authorization protocols might not take this into account. Choosing the wrong drug initially can result in delays in disease control resulting in increased cost of care, missed opportunity to intervene, and increased rate of surgery. Delays in treatment are also an issue because the medications are not as effective with worsening inflammation.

Biomarkers would be helpful in making an earlier diagnosis, but they are not yet specific enough. For example, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are nonspecific measures of inflammation. Stool calprotectin is a nonspecific stool test for inflammation with a high positive predictive value for inflammation (infectious or inflammatory) and high negative predictive value for lack of any inflammation.

Current personalized treatment options are to consider patient, disease, and medical history factors in selecting therapy. The goal of treatment is to achieve no evidence of disease, or at least a minimum of disease activity. Goal achievement should be assessed with imaging or colonoscopy to prove that there is disease remission and not just symptom remission.

Therapeutic drug monitoring should also be used when available. Future options for personalized medicine are to determine how the immune system is activated in a particular patient to identify which medication is best to utilize and to use combinations of medications to suppress active inflammation and then withdraw therapies to single drug or complete cessation of therapy when in remission.

Managed care can improve IBD treatment by targeting patients who are chronically receiving steroid therapy for a switch to a steroid-sparing agent, such as a biologic. Some strategies for reducing chronic steroid use include developing a system to identify all patients on corticosteroids,

Exhibit 2: Safety and Efficacy in Clinical Context

Drug	Safety	Efficacy	Patient with UC	Patient with CD	Miscellaneous Information
Mesalamine	Safest	Medium	Only Mild/Moderate	Maybe Mild Colonic CD (In General No Role In CD)	Overused In CD No Role In Moderate to Severe No Role As Combo Therapy
Thiopurines	Medium Risk	Low	Rarely used alone, mostly as combo therapy now.	Rarely used alone, mostly as combo therapy now.	Rarely used as initial therapy Risks increased when used as combo therapy
Anti-TNF	Low Risk	HIGH (Infliximab)	Moderate to severe	Fistulizing CD Perianal CD Moderate to severe	Most effective Can be used as combo or check drug levels. Infliximab most effective
Vedolizumab	Very Safe	Medium	Moderate Moderate to severe with comorbidities	Moderate Inflammatory CD	Safest Drug Not so effective In CD
Ustekinumab	Low Risk	Medium		Moderate to severe CD	Effective on par with anti-TNF
Tofacitinib	High Risk	Medium	Moderate to severe		Try to lower to 5mg BID

Exhibit 3: Selected Investigational Agents for IBD

	Target	Disease	Route	Phase
Ertolizumab	Anti-integrin β7 subunit of the heterodimeric integrins α4β7 and αEβ7	CD/UC	Monthly subcutaneous	III
AJM-300	α4 integrin antagonist	UC	Oral	III
Ozanimod	Sphingosine 1-phosphate receptor modulator	CD	Oral	III (already approved for multiple sclerosis)
PRV-300	anti-toll-like receptor 3 monoclonal antibody	UC	Intravenous	Ib
Risankizumab	Monoclonal antibody against the p19 subunit of IL-23	CD	Intravenous	III (already approved for psoriasis)
Filgotinib	JAK 1 inhibitor	UC/CD	Oral	II/III
Upadacitinib	JAK 1 inhibitor	UC/CD	Oral	II/III (already approved for rheumatoid arthritis)

educating and empowering the patients with checklists for quality care, educating physicians about quality metrics in IBD, and streamlining the process by which steroid-sparing agents are ordered. A pharmacist, pharmacy technician, or medical assistant could perform all authorizations. Plans can provide physician incentives to improve compliance (or consider punitive approach) with prescribing steroid-sparing agents.

Another area where managed care can improve care is in encouraging medication adherence. Thirty to 45 percent of patients with IBD are nonadherent to their treatment regimen.[12,13] Predictors of nonadherence for males are a UC diagnosis and employment status. Predictors for females are age less than 30. Medication cost was a relevant predictor for both men and women. The nonadherent patient is less likely to achieve long-term disease remission and thus likely to cost more in total health care costs.

Even with current biologic therapies, not all patients are able to achieve disease remission. There are numerous agents under investigation for IBD which will hopefully continue to improve outcomes. There are currently 274 studies for UC and 294 for CD listed on clinicaltrials.gov that are active, Exhibit 3 presents information on some selected investigational agents.

Conclusion

Ulcerative colitis and Crohn's disease are different diseases and thus may require different treatment. Personalized medication selection should be based on patient factors, disease subtype and severity, and the medication mechanism of action. No longer should a stepped approach be used for therapy, nor should a requirement for failure of older therapies be required before advancing to a biologic.

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Therapeutic Switching and Sequencing in Multiple Sclerosis: Implementing Expert Strategies for Improved Clinical and Economic Outcomes

Robert A. Bermel, MD, MBA

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

Summary

Multiple sclerosis (MS) is a disabling disease of the young, but there has been a revolution in the treatment over the past 20 years. There are now numerous disease-modifying therapies (DMTs) that are changing the natural history of this disease.

Key Points

- Numerous DMTs are available for treating MS.
- The goals of treatment with DMTs are to prevent disability and conversion to secondary-progressive disease.
- No evidence of disease is the target to aim for with treatment.
- Initiating high-efficacy DMTs initially reduces disability accumulation compared to initiating lower efficacy DMTs and then escalating therapy.

MULTIPLE SCLEROSIS (MS) IS A CHRONIC autoimmune demyelinating disease of the central nervous system with onset in young and middle adulthood, and it is the most common non-traumatic cause of disability among young people in the Western Hemisphere. Approximately a million individuals are affected in the United States (U.S.). Unfortunately, people who have an episode of neurologic symptoms suggesting demyelination may not seek care because the symptoms go away, but the episode leaves residual damage. MS is an unpredictable, heterogeneous disease; some with the disease have a severe course, whereas others will have a mild course; however, at this point, clinicians cannot yet identify which patient will have which course.

The most common form of MS is relapsing-remitting (RRMS), where there are relapses interspersed with periods of symptom remission. Without treatment, there is increasing disease burden and disability and many patients have disease transformation into secondary-progressive (SPMS). The least common type of MS is primary-progressive (PPMS). It is important to understand that both relapse and progression in MS are driven by inflammation (Exhibit 1).[1] Therapies that reduce immune system activity can target both relapses and disability progression. An acute relapse is treated with high-dose corticosteroids. Disease-modifying therapy (DMT) is used to reduce the risk of relapse and slow disease progression. Acute inflammation can be easily detected on an MRI and based on symptoms, but chronic inflammation is harder to detect and measure. Aging also impacts accumulation of disability; aging with MS is even harder than aging alone.

The available DMT for treating RRMS represent a range of mechanisms of action which target different aspects of the immune system and/or response (Exhibit 2). Clinicians are well-equipped to treat and monitor the inflammatory component of RRMS with 16 approved therapies and widespread availability of MRI for monitoring DMT efficacy, even though it is an imperfect tool. DMTs are variably effective in individuals, and there is no biomarker to prospectively predict efficacy of specific treatments in individual patients; therapy really is trial and error. Importantly, the available treatments are effective in RRMS but not with progressive disease and do not restore damaged tissue. Monitoring on therapy (clinically and with

Exhibit 1: Both Relapses and Progression are Driven by Inflammation[1]

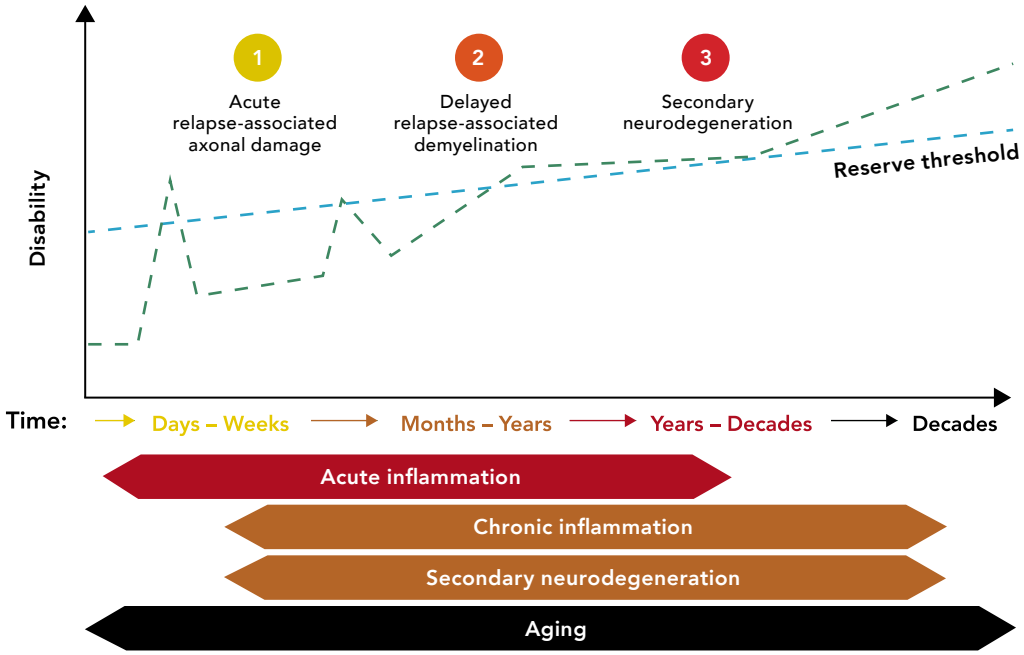


Exhibit 2: RRMS Therapeutic Landscape

Mechanism	Agents
Immunomodulation	***Self-injection*** interferon-beta, glatiramer acetate, ***Oral*** dimethyl fumarate, diroximel fumarate
Inhibition of cell replication	***Oral*** Teriflunomide
Cell depletion	***Infusion*** alemtuzumab, ocrelizumab ***Oral*** cladribine
Altered cell trafficking	***Infusion*** Natalizumab ***Oral*** fingolimod, siponimod

MRI) is common, though there are no standards or defined targets in the clinic. Performance assessment and standard measures of quality of life, in addition to standard questioning about symptoms and general functioning, can help improve assessment and is done in some MS clinics. The American Academy of Neurology (AAN) publishes treatment guidelines to help clinicians in selection and monitoring of DMT.[2] Early treatment of MS is important to prevent neurologic damage. With MS, there is a preclinical period where patients are having damage done to the central nervous system (CNS), which may or may not result in symptoms. Once a patient has an episode of symptoms that gets them a diagnosis, they already have evidence of damage on MRI. The clinical course of symptomatic RRMS is episodes of symptoms (relapses) interspersed with remission, but over time the patient does not go back to their prior functional baseline after a relapse. Without adequate treatment, many patients ultimately evolve into a secondary- progressive course, with some degree of permanent disability. The current treatment strategy is to start DMT as early as possible to prevent disability accumulation and conversion to SPMS and to maximize long-term outcomes (neurologic function and health-related quality of life).

The ability to predict prognosis in individual patients is limited. Clinical features correlate poorly

with the ongoing inflammation and resultant irreversible tissue destruction in RRMS. MRI evidence of disease activity happens about 10 times as often as symptomatic relapses. Features suggesting a poor prognosis and need for early definitive therapy include frequent relapses, particularly if severe, with incomplete recovery, and with resultant increasing impairment; substantial MRI lesion burden, repeatedly active MRI scans with increasing lesion burden, continued disease activity despite treatment with a standard agent, and brain atrophy on initial evaluation.

Treat-to-target in MS is a concept borrowed from rheumatoid arthritis. The target in MS is no evidence of disease activity (NEDA) and the complete absence of detectable disease activity while on DMT. This means no new MRI lesion activity (gadolinium-enhancing lesions, new or enlarged T2 lesions), no clinical relapses, and no disability worsening. NEDA rates are increasingly reported in clinical trials and it is being utilized in practice.

For many years, interferon beta (IFNβ) and glatiramer acetate (GA) injections were the backbone therapies for MS. These agents have a good safety and extensive track record, and some patients do well on them. Unfortunately, they have modest efficacy, and many patients continue to have relapses. MRI lesion activity at six to 12 months after starting IFNβ predicts an inadequate treatment response long-term.[3] Selected patients may benefit from switching between classes, but never should be switched among IFNβs. If there is still MRI activity, the patient should be moved to a more potent agent. Patients dislike the frequent injections and bothersome adverse events with these two classes. Use of IFNβ or GA as initial therapy for RRMS patients is becoming rare. Given the modest efficacy and adverse events, taking the time to see if these agents work is a tough sell to patients in most MS clinics.

Dimethyl fumarate (Tecfidera®), an oral DMT, has immunomodulatory and cytoprotective effects and reduces annual relapse rate (ARR) and MRI activity.[4,5] Gastrointestinal (GI) and flushing adverse events limit the use of this agent in about one-third of patients. Diroximel fumarate (Vumerity®) has the same mechanism of action as dimethyl fumarate but has a distinct chemical structure that has been shown to have fewer reported GI adverse events. Both agents are metabolized to monomethyl fumarate (MMF), which is the active agent.

Teriflunomide (Aubagio®) is the active metabolite of leflunomide, which is used to treat rheumatoid arthritis. It blocks dihydro-orotate dehydrogenase which inhibits de novo pyrimidine synthesis in rapidly dividing cells. T and B cells are rapidly dividing cells; thus, this agent inhibits T-cell and B-cell proliferation. This agent reduces ARR by 30 percent.[6-8] This is a well-tolerated, once-daily oral medication which is used sometimes for those with milder MS. Teratogenicity is a major issue so it is not used in women of childbearing age.

Fingolimod (Gilenya®) is an oral sphingosine 1-phosphate receptor modulator which prevents lymphocytes from leaving lymph nodes, thus reducing the number of lymphocytes entering the bloodstream and CNS compartment. This agent initially stimulates and then down-modulates sphingosine-1-phosphate receptor 1 (S1P1).[9] Fingolimod treatment produces about a 54 percent reduction in ARR and has shown benefit in reducing brain atrophy and MRI activity.[10-12] This agent does require monitoring with the first dose because of effects on the heart rate. Fingolimod is a once-daily oral agent that works well in about 60 percent of patients with minimal significant adverse events.

In a real-world analysis of data from two MS centers, discontinuation was more common in those treated with dimethyl fumarate (44.2%) compared to fingolimod (34.8%) over 24 months (odds ratio [OR] 1.55, 95 percent confidence interval [CI] 1.21 to 1.99, $p < 0.001$).[13] The leading cause for discontinuation was intolerability for both (56.1% versus 46.2%, respectively). The proportion of patients with clinical relapses was low for both medications (15.1% versus 13.1%). There was no difference in the proportion of patients with relapses (OR 1.27, 95% CI 0.90 to 1.80, $p = 0.174$), gadolinium-enhancing lesions (OR 1.42, 95% CI 0.92 to 2.20, $p = 0.114$), or new T2 lesions on brain MRI (OR 1.13, 95% CI 0.83 to 1.55, $p = 0.433$). The author concluded that dimethyl fumarate and fingolimod have similar effectiveness in a large, two-site clinical population over 24 months. Discontinuation of both DMTs was common and occurred more frequently with dimethyl fumarate. This study is a great example of real-world evidence on how DMT performs.

Siponimod (Mayzent®) is a more selective S1P receptor modulator than fingolimod. It binds to S1P receptors 1 and 5. Siponimod also crosses the blood-brain barrier (BBB) and may have direct neuroprotective effects in the CNS. In the clinical trials, siponimod appeared to have the most benefit for patients who were younger, had gadolinium-enhancing lesions, lower disability, and shorter disease duration.[14,15]

Both fingolimod and siponimod can cause bradycardia and are contraindicated in patients with certain cardiac diseases. Fingolimod requires first-

dose monitoring for bradycardia for six hours for all patients; first-dose monitoring is recommended with siponimod for patients with sinus bradycardia, first- or second-degree (Mobitz type I) atrioventricular (AV) block, or a history of myocardial infarction or heart failure.

Cladribine (Mavenclad®) is an immunosuppressive purine antimetabolite agent that has cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes. The NEDA rate at 96 weeks is 28 percent better than placebo.[16] The recommended cumulative dosage of oral cladribine is 3.5 mg/kg of body weight divided into two yearly treatment courses (1.75 mg/kg per treatment course). Each treatment course is divided into two treatment cycles of four or five days, separated by approximately four weeks.

Natalizumab (Tysabri®) prevents activated T cells and monocytes from crossing the BBB into the CNS by binding to the α4-subunit of α4β1 and α4β7 integrins expressed on the surface of all leukocytes except neutrophils and inhibiting the α4-mediated adhesion of leukocytes to their counter-receptors. This agent is given as an infusion every four weeks and is one of the most effective agents in treating MS. In a long-term, open-label, single-arm trial, the NEDA rate was 75.4 percent at four years of treatment.[17] The adverse event of major concern with natalizumab is progressive multifocal leukoencephalopathy (PML), caused by John Cunningham virus (JCV) infection. Prevention of lymphocytes entering the CNS can lead to brain infections such as PML. Patients must be tested for JCV antibodies prior to and every three months during use. If the patient is JCV(+), clinicians will use natalizumab in some circumstances, especially if the titer is low and there is no history of immunosuppression, but will restrict use to one to two years.

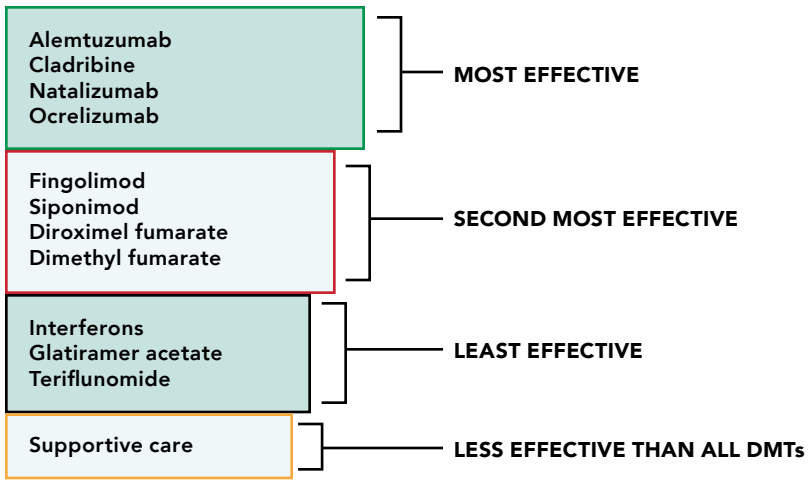
Alemtuzumab (Lemtrada®), a humanized monoclonal antibody that targets CD52, produces rapid, profound, and prolonged lymphocyte depletion with a gradual reconstitution with altered cell profile and function. Giving this agent is essentially a reset of the immune system. B cells and monocytes come back months before T cells (3 to 8 months versus 30 to 60 months). After treatment, there is a sustained decrease in CD4+T cells greater than CD8+ T cells and regulatory T cells are relatively enriched. This agent is given as a daily infusion for five days and then one year later it is given daily for three days. After that, it is only given if the patient shows disease breakthrough, which may be years later. Advantages of this agent are potent efficacy and convenience of annual administration but there are safety concerns during infusion (intracerebral hemorrhage) and after therapy, a complicated start-up process, and required ongoing monitoring. Thus, it is used less frequently than other agents. After treatment, patients have to have complete blood count for autoimmune cytopenia and urinalysis to check for glomerular nephropathy monthly for four years, thyroid stimulating hormone (TSH) every three months for four years, periodic liver function tests, and annual skin exams (melanoma). An Institute for Clinical and Economic Review (ICER) review showed this was one of the most cost-effective regimens because of its potency and limited administration.[18] The principal use of this medication is for patients with active relapsing MS who have failed several other therapies.

Ocrelizumab (Ocrevus®) has been one of the most exciting therapies. It selectively depletes B cells when given by infusion every six months. It is similar to rituximab (> 90% epitope overlap) which has been studied in MS and is sometimes used off-label for MS. Ocrelizumab is humanized instead of chimeric like rituximab, has a different though overlapping antigen site, and more potent effect on antibody-dependent cell-mediated cytotoxicity and apoptosis. Since ocrelizumab is a humanized monoclonal antibody, it is less immunogenic than rituximab and better tolerated. It is very effective in reducing ARR (46% reduction compared to IFNβ) and preventing MRI lesions; has a safety profile similar to IFNβ; and has become one of the most commonly used agents.[19] In a long-term extension trial of PPMS treatment, ocrelizumab reduced the rate of those who end up in a wheelchair compared to placebo.[20] This agent is the only treatment FDA approved for PPMS in addition to RRMS. Infections and immunoglobulin depletion are the two adverse events that appear to be an issue with this agent.

Ofatumumab, another B-cell depleting therapy already approved for treating chronic lymphocytic leukemia, will likely be the next agent approved for treating MS. The FDA recently delayed review of ofatumumab for this indication until September 2020.[21] This subcutaneously administered B-cell therapy reduced ARR by 50.5 percent (0.11 versus 0.22) and 58.5 percent (0.10 versus 0.25) compared to teriflunomide ($p < 0.001$) in ASCLEPIOS I and II studies respectively.[22] Based on the available data, it appears to have similar efficacy to ocrelizumab.

Exhibit 3 compares the relative efficacy of the various agents.[2,16,18,23] NEDA rates with the most potent agents are approximately 30 percent better than placebo and 15 to 20 percent better than interferon (alemtuzumab and ocrelizumab, respectively).[16,18,19] There are two different

Exhibit 3: DMT Effectiveness[2,16,18,23]



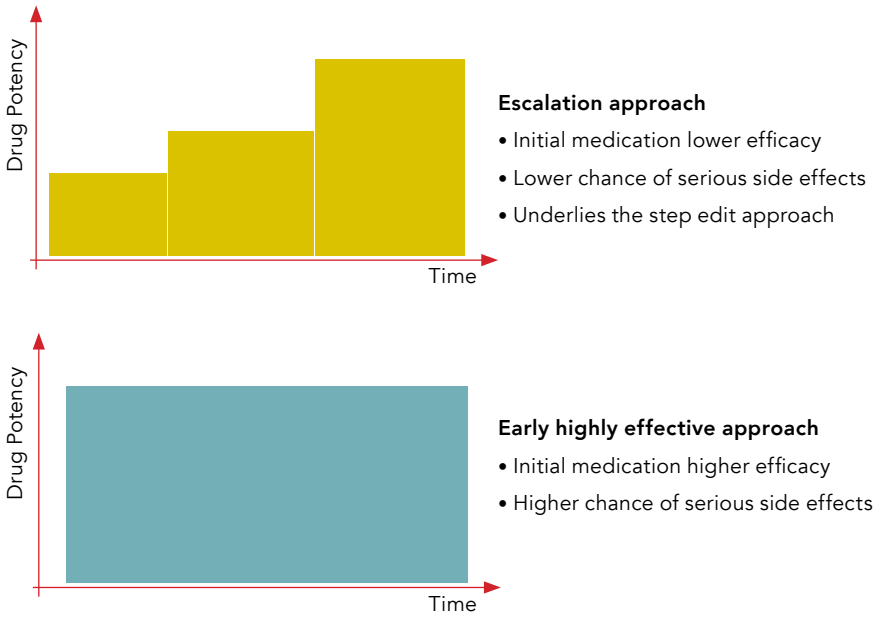
approaches for starting therapy; the first is the traditional approach of escalation where a less potent, but typically safer agent, is started first (Exhibit 4). The escalation method underlies many managed care step-edit programs. The other approach is to start therapy with a high-efficacy agent, which has higher risk of serious adverse events. In real-world cohorts, early high-efficacy therapy slows disability progression, whereas 60 percent of the escalation approach patients experienced disability accumulation prior to escalation.[24] Additionally, long-term in RRMS, there is a lower risk of conversion to SPMS with high-efficacy therapy.[25] Escalation protocols and contemporary surveillance strategies may be insufficiently responsive to making needed therapy changes in a timely manner, which may account for the difference in disability progression and conversion rates. First-line high-efficacy DMT adoption has been slow and is still a minority practice (~33% of new cases in 2018).[26] Two randomized comparison trials are in progress to better determine the differences between escalation and early high-efficacy therapy.

Neurofilament light (NfL), an emerging biomarker in MS, is a cytoskeletal component of neurons released into the spinal fluid and into the blood with neuronal (especially axonal) injury or death. It is now measurable in blood with high sensitivity and precision. NfL in serum correlates with brain atrophy and increased disability risk. Serum NfL has also been shown to correlate with NEDA, adding to its potential value as a sensitive and clinically meaningful biomarker of progression and end-organ damage in MS.[27,28] Validation studies in large numbers of patients are ongoing.

A major issue in management of MS for clinicians, patients, and managed care is the escalating price of medications. Prices of MS DMT have continued to escalate, with the rate of increase dramatically exceeding other biologics and specialty drugs.[29] Given the unsustainability of these price increases, it is important to enhance the value of DMT in MS care. Several ways to enhance value are to avoid waste and unnecessary services, target DMT overuse especially in those misdiagnosed, reduce overuse of necessary services, and shift services to lower-cost settings. Utilization of shared medical visits, telemedicine visits, and homecare services can help lower costs.

Treating relapses with oral, high-dose steroids at home instead of intravenous infusion in various settings is a major cost-saving intervention, much more convenient for patients, and just as effective. Health systems and managed care need to leverage multidisciplinary care to target common, but undertreated, causes of disability (depression, fatigue) in MS. Neurologists and DMT are not the best ways to deal with these sources of disability. It is important to identify patients who may have been misdiagnosed with MS and are inappropriately being treated with DMT. In a 2012 survey of 122 MS subspecialists, 34.4 percent reported seeing six or more misdiagnosed patients in the last year, including 17.2 percent who had seen 10 or more such patients.[30] Almost 65 percent of the survey respondents estimated that more than a quarter of

Exhibit 4: Different Treatment Approaches in MS



all the misdiagnosed patients they had seen were on DMT for MS. An easy value-enhancing intervention is to make sure those who start on a DMT meet the criteria for MS. Another way to enhance value and reduce costs may be to discontinue therapy later in life when the disease has become quiestant.[31] There is a large clinical trial ongoing examining treatment discontinuation after age 60.

The Cleveland Clinic MS program has been able to contain costs for their employee health plan by leveraging their advanced CarePaths and partnering with payers to design evidence-based step therapies and prior authorization policies that steer patients toward the right care at the right time, while maximizing positive outcomes. Cleveland Clinic has been able to flatten their per member per month costs of the patients within their employee health plan without adversely affecting outcomes.

Conclusion

MS is an unpredictable, but very disabling disease. There are now numerous effective treatments which all have advantages and disadvantages. The best therapy for a given patient must be determined through careful consideration of numerous factors. Current controversies in management are whether to use an escalation or high-efficacy approach to DMT and how to contain costs while enhancing value.

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Managing Insomnia: Optimal Treatment Goals to Improve Outcomes

Karl Doghramji, 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

Insomnia is a prevalent condition that significantly impacts patient health and well-being. In addition to identifying and treating comorbidities which may be causing or worsening sleep issues, management of the insomnia can be accomplished with cognitive behavior therapy and medications.

Key Points

- Insomnia is quite common and has major consequences.
- Management begins with a systematic evaluation.
- Treatment of comorbidities that contribute to insomnia is necessary.
- Insomnia can be directly managed by cognitive behavioral therapy and pharmacological agents.

INSOMNIA IS A COMMON SLEEP PROBLEM for adults. The National Institute of Health estimates that roughly 30 percent of the general population complains of sleep disruption, and approximately 10 percent have associated symptoms of daytime functional impairment consistent with the diagnosis of insomnia.[1] In a National Sleep Foundation poll, more than half of people reported at least one symptom of insomnia a few nights per week within the past year.[2] Thirty-three percent said they had at least one of these symptoms every night, or almost every night in the past year. Similarly, about half of primary care patients report insomnia issues.[3]

Despite high rates of insomnia, few patients discuss this issue with their care providers. In one survey, of the 664 respondents who reported difficulty sleeping, 70 percent reported having never discussed their problem with a physician.[4] Of the 30 percent who reported having discussed their problem with a physician, 24 percent indicated that insomnia was not the primary reason for their consultation. Only 6 percent reported that they had sought the help of a physician for their sleep difficulty and that it was the primary reason for their consultation. In a study of the prevalence, severity, and predictors of insomnia in hospitalized psychiatric patients, 79.4 percent of the patients met the criteria for insomnia, but it was not mentioned as a clinical problem in the discharge notes problem list for any of these patients.[5] Multivariate analysis indicated that age ($p = 0.009$), recent suicide attempt or ideation ($p < 0.001$), tobacco use ($p = 0.024$), and recreational drug use during the past month ($p = 0.040$) were significant predictors of insomnia severity.

The negative outcomes of insomnia are substantial (Exhibit 1).[6-12] Individuals with insomnia exhibit performance impairments for several cognitive functions, including working memory, episodic memory, and some aspects of executive functioning.[12] An interesting study in a driving simulator found that those with insomnia had significant impairment in terms of lane positioning and in the number of inappropriate lane crossings they made within 20 minutes of starting to drive, compared to those who did not have insomnia.[13]

There is an increased prevalence of medical disorders in individuals with insomnia.[14] Hypertension, breathing problems, urinary problems, chronic pain, and gastrointestinal problems are the most common. These may be a

Exhibit 1: Negative Outcomes Associated with Insomnia[6-12]

- Diminished ability to enjoy family and social relationships
- Decreased quality of life
- Increased absenteeism and poor job performance
- Motor vehicle crashes
- Increased risk of falls
- Increased health care costs
- Impaired cognitive function including concentration and memory
- Increased incidence of pain
- Hypertension
- Diabetes
- Increased mortality
- Enhanced risk of present and future psychiatric disorders (especially depression)

consequence of the underlying insomnia, or they may exacerbate or cause insomnia.

The diagnostic criteria for insomnia disorder are dissatisfaction with sleep quantity or quality with one or more of the following:

- difficulty initiating sleep
- difficulty maintaining sleep
- early morning awakening with inability to return to sleep.[15]

Other criteria include the following:

- The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.
- The sleep difficulty occurs at least three nights per week.
- The sleep difficulty is present for at least three months.
- The sleep difficulty occurs despite adequate opportunity for sleep.
- The insomnia cannot be explained by and does not occur exclusively during another sleep–wake disorder.
- The insomnia is not attributable to the physiological effects of a drug of abuse or medication.
- Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.

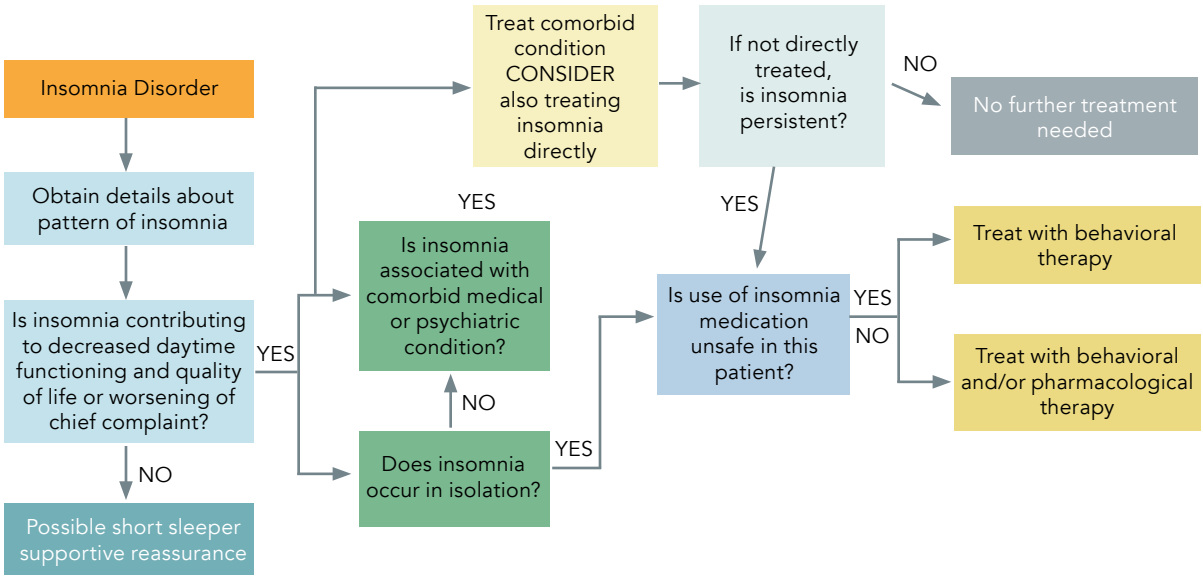
The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) makes no distinction between primary and comorbid insomnia.[15] Initiation insomnia (prolonged sleep latency) can be caused by irregular waking times or shift work, delayed sleep phase disorder, daytime stimulants/caffeine, and restless legs syndrome. Maintenance insomnia (sleep discontinuity) can be related to depression, sleep apnea syndrome, and periodic limb movements in sleep. Terminal insomnia (early morning awakening) can be related to depression, advanced sleep phase disorder, and shiftwork disorder.

Treatment approaches include addressing the comorbid condition with specific treatments, directly treating the insomnia disorder, or simultaneously treating both. Comorbid condition treatments include such things as continuous positive airway pressure (CPAP) for obstructive sleep apnea, antidepressants for major depression, proton pump inhibitors for gastroesophageal reflux disease (GERD), and mood stabilizers for mania, and medication change for iatrogenic insomnia. An example would be scheduling diuretic medications or activating medications in the morning instead of evening, so they are less likely to affect sleep. Directly treating the insomnia disorder can be with cognitive behavioral therapy (CBT), pharmacological agents, or both. Ideally, both are used. Exhibit 2 presents an insomnia evaluation and management algorithm.[16]

Numerous CBT interventions are possible (Exhibit 3).[17,18] There are numerous sleep hygiene interventions which are relatively easy for patients to institute and can help improve the sleep and the sleep environment (Exhibit 4). CBT is supported by numerous studies. In a meta-analysis of 20 trials that incorporated at least three of the following (cognitive therapy, stimulus control, sleep restriction, sleep hygiene, and relaxation) sleep onset latency was improved by 19.03 (95% confidence interval CI, 14.12 to 23.93) minutes, awake after sleep onset was improved by 26.00 (CI, 15.48 to 36.52) minutes, total sleep time was improved by 7.61 (CI, 0.51 to 15.74) minutes, and sleep efficiency was improved by 9.91 percent (CI, 8.09% to 11.73%).[19] Changes seemed to be sustained and no adverse outcomes were reported.

Despite evidence of CBT effectiveness, patients are rarely referred for this treatment, especially in primary care. Three major barriers to CBT use are limited access to providers, inadequate primary care screening and appropriate referring, and patient-related issues.[20] Primary care clinicians may not

Exhibit 2: Insomnia Evaluation and Management Algorithm[16]



consider CBT due to of lack of knowledge on the subject, its effectiveness, treatment beliefs, and their lack of motivation, as prescribing a medication is much easier. Limited or no insurance reimbursement for CBT is a major barrier for patients.

Surveys have shown that many people self-treat their insomnia with valerian, melatonin, over-the-counter sleep and cold medicines containing diphenhydramine, doxylamine, or other antihistamines with anticholinergic properties, and many other alternative medications of questionable value. The evidence for efficacy for most of these is limited. For some patients, antihistamines work fine for occasional use to get to sleep. The use of antihistamines with anticholinergic effects is associated with increased brain atrophy and dysfunction and clinical decline in older patients; therefore, the use of over-the-counter antihistamines for sleep among the elderly should be discouraged.[21] In 19 placebo-controlled studies in 1,683 participants, melatonin has demonstrated efficacy in modestly reducing sleep latency (7.06 minutes), increasing total sleep time (8.25 minutes), and improved sleep quality (standardized mean difference = 0.22).[22] The effects on sleep latency and sleep duration are magnified with sustained-release products and higher doses. There are some concerns regarding potential adverse events with long-term use.

Prescription pharmacotherapy for insomnia consists of both agents approved by the FDA for insomnia and those which are approved for other indications but have sedating properties. Agents that are not FDA approved for insomnia but are frequently used include sedating antidepressants, antipsychotics, and anticonvulsants. FDA-approved hypnotics include benzodiazepine receptor agonists and the non-benzodiazepines (melatonin receptor agonist, H1 receptor antagonist, and orexin receptor antagonists). Hypnotic medications are approved for reduction in sleep latency, enhancement of sleep maintenance, or both.

Sedating antidepressants (trazodone, mirtazapine, paroxetine) used in low doses at bedtime have low abuse risk and a large dose range for safety. Efficacy is not well established for insomnia. Additionally, these agents can cause adverse events, including daytime sedation, anticholinergic effects, and weight gain.

Low doses of atypical antipsychotics (quetiapine, olanzapine) have low abuse potential and are sedating. At appropriate doses, these are effective for psychotic disorders and may be most useful when these disorders are also present. Disadvantages of antipsychotics include not being well investigated in insomnia, adverse events of daytime sedation, anticholinergic effects, weight gain, hyperglycemia and lipid abnormalities, and risk of extrapyramidal symptoms and tardive dyskinesia.

Benzodiazepines approved for insomnia include triazolam, temazepam, estazolam, flurazepam, and quazepam. All of these are labeled for short-term use only. The benzodiazepine receptor agonists include

Exhibit 3: Psychological and Behavioral Treatments for Insomnia[17,18]

Techniques	Method
Stimulus control therapy*	If unable to fall asleep within 20 minutes, get out of bed, do boring activity until sleepy and repeat as necessary
Relaxation therapies*	Biofeedback, progressive muscle relaxation
Restriction of time in bed (sleep restriction)	Decrease time in bed to equal time actually asleep and increase as sleep efficiency improves
Cognitive therapy	Talk therapy to dispel unrealistic and exaggerated notions about sleep
Paradoxical intention	Try to stay awake
Sleep hygiene education	Promote habits that help sleep; eliminate habits that interfere with sleep
Cognitive-Behavioral Therapy*	Combines sleep restriction, stimulus control and sleep hygiene education with cognitive therapy

*Standard Treatment according to American Academy of Sleep Medicine

Exhibit 4: Good Sleep Hygiene

Things to Avoid	Thing to Do
• Alcohol	• Get out of bed at the same time every morning
• Caffeine, nicotine, and other stimulants	• Increase exposure to bright light during the day
• Exposure to bright light during the evening and night hours	• Establish a daily activity routine
• Exercise within 3 hours of bedtime	• Exercise regularly in the morning and/or afternoon
• Heavy meals or drinking within 3 hours of bedtime	• Set aside a worry time
• Using your bed for things other than sleep (or sex)	• Establish a comfortable sleep environment
• Napping, unless a shift worker	• Do something relaxing prior to bedtime
• Watching the clock	• Try a warm bath
• Trying to sleep	
• Noise	
• Excessive heat/cold in room	

zaleplon (Sonata®), zolpidem (Ambien®, Ambien CR®, generics), and eszopiclone (Lunesta®). There are also sublingual (Intermezzo®, Edluar®) and oral spray zolpidem (Zolpimist®). These benzodiazepine receptor agonists decrease sleep latency and increase total sleep time. Only zolpidem extended release and eszopiclone have been shown to decrease being awake during the night. Eszopiclone has been shown to improve patient-reported daytime function.[23] All of the benzodiazepines and benzodiazepine receptor agonists are DEA schedule IV controlled agents.

Ramelteon is a melatonin receptor agonist that has been shown to decrease sleep latency. A low-dose formulation of doxepin (Silenor®), an antidepressant which is a histamine 1 receptor antagonist, is now FDA approved for treating insomnia. The insomnia dose is 3 to 6 mg 30 minutes before bedtime compared to the antidepressant dose of 150 to 300 mg daily. It decreases time awake during the night. Doxepin and ramelteon are the only hypnotics which are not schedule IV controlled agents.

Orexins are neuropeptides that regulate arousal, wakefulness, and appetite. Elevated plasma orexin-A levels have been shown in insomnia disorder.[24] A lack of orexin in the brain due to destruction of the cells that produce it leads to type 1 narcolepsy.[25] Blocking

Exhibit 5: Adverse Events with Hypnotics

Benzodiazepine receptor agonists (benzodiazepines, eszopiclone, zaleplon, zolpidem)
• Daytime sedation, psychomotor and cognitive impairment (depending on dose and half-life) • Rebound insomnia • Respiratory depression in vulnerable populations
Melatonin receptor agonist (ramelteon)
• Headache, somnolence, fatigue, dizziness
H_1 receptor antagonist (doxepin)
• Somnolence/sedation, nausea
Orexin receptor antagonist (lemborexant, suvorexant)
• Somnolence • Risk of impaired alertness and motor coordination, including impaired driving; increases with dose • Contraindicated in narcolepsy

the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is thought to suppress the wake drive. Suvorexant (Belsomra®) was the first dual orexin receptor antagonist (DORA) to be approved by the FDA for insomnia in 2014. It decreases sleep latency, time awake during the night, and total sleep time and is a schedule IV controlled agent. Lemborexant (Dayvigo®) is the newest approved sleep medication which was approved in late 2019 and is also a DORA. It has been shown to improve sleep latency and continuity in insomnia and is also a schedule IV controlled agent.[26,27] Studies with this agent are underway for irregular sleep-wake rhythm disorder and mild to moderate Alzheimer's dementia. The two DORA have not been compared with each other.

Adverse events of the prescription agents are shown in Exhibit 5. In 2019, the FDA added a boxed warning regarding complex sleep behavior to package labeling for eszopiclone, zaleplon, and zolpidem.[28] It was also added to avoid use in patients who have previously experienced an episode of complex sleep behavior (sleepwalking, sleep driving, and engaging in other activities while not fully awake) with any of these agents. Serious injuries and death from complex sleep behaviors have occurred in patients with and without a history of such behaviors, even at the lowest recommended doses, and the behaviors can occur after just one dose. These behaviors can occur after taking these medicines with or without alcohol or other central nervous system depressants that may be sedating, such as tranquilizers, opioids, and anti-anxiety medicines. Over 60 cases have been reported and included accidental overdoses, falls, burns, near drowning, exposure to extreme cold temperatures leading to loss of limb, carbon monoxide poisoning, drowning, hypothermia, motor vehicle collisions, and self-injuries such as gunshot wounds and apparent suicide attempts. Nonfatal sleep behaviors have included preparing and eating food, making phone calls, or having sex. Patients usually did not remember these events. The underlying mechanisms by which these insomnia medicines cause complex sleep behaviors are not completely understood.

In choosing between pharmacotherapy or CBT, clinicians can consider the following points. Pharmacotherapy would be the choice if there is short-term insomnia, a lack of specific cognitive or behavioral factors in the patient, a need for rapid improvement, time limitations (e.g., during hospitalization), limited patient finances, or lack of trained therapists.[29] CBT would be the first therapy of choice if there is chronic insomnia, a need for sustained clinical improvement, history of or present substance use or abuse, multiple comorbid medical conditions, or chronic hypnotic use being discontinued.

In general, CBT should be the initial treatment option in persons with chronic insomnia.[30,31] Medication should be reserved for occasional adjunctive treatment in chronic insomnia. The choice to use medications should be based on shared decision-making, with prescriptions limited to five weeks or less. Benzodiazepines should not be used in older adults as a first choice for insomnia, agitation, or delirium.[31] Clinicians should also avoid prescribing antipsychotic medications as a first-line intervention

for insomnia in adults unless there is another reason for using the antipsychotic medications.

Medications with a possible favorable effect on comorbid conditions can be chosen. In patients who have sleep issues after alcohol discontinuation, trazodone improves sleep without affecting relapse. With post-traumatic stress disorder (PTSD), prazosin, an alpha-1 adrenergic antagonist antihypertensive, improves sleep, nightmares, and daytime symptoms. Eszopiclone has been shown to improve sleep and daytime PTSD symptoms, pain in those with rheumatoid arthritis, and decreased waking due to hot flashes. Zolpidem increased sleep and energy in a small study in fibromyalgia. For those with a history of substance abuse, ramelteon and doxepin have the lowest abuse potential.

Another consideration in selecting therapy is whether the patient has difficulty getting to sleep (initiation insomnia) or staying asleep (maintenance insomnia). Zaleplon, zolpidem, and ramelteon are good choices for initiation insomnia. For those with maintenance insomnia, doxepin and sublingual zolpidem can be chosen. For the patient with both initiation and maintenance issues, zolpidem extended release, eszopiclone, suvorexant, and lemborexant are options for treatment. Other issues in choosing a therapy include prior failure of medications, patient preference, and cost.

An interesting non-pharmacological option is frontal cerebral thermal therapy (Ebb), which is a headband that cools the forehead (57-61°F) continuously throughout the night, which is thought to reduce brain hyperarousal. At the brain metabolic level, hyperarousal sleep can be associated with increased cerebral metabolism, especially across the frontal cortex. The company also offers a once-weekly, four-week telephone and digitally-based CBT program led by National Board-Certified Health and Wellness coaches to complement the device. In a placebo (sham device) controlled clinical trial and open label trials, the Ebb device produced improvements on measures of sleep latency in those with insomnia and menopausal related sleep issues.[32-36] The cost for the device is $400, with approximtely $200 yearly for replacement of cooling fluid and headband, and $199 for the coaching program.

Conclusion

Insomnia is highly prevalent. It is associated with psychological and physical impairments and enhances the risk of other conditions. Management begins with a systematic evaluation followed by treatment of comorbidities and then the insomnia. Insomnia can be directly managed by cognitive behavioral therapy and pharmacological agents.

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Strategies for Improving Patient Outcomes through Optimal Treatment and Management of Major Depressive Disorder

Alan F. Schatzberg, 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

Managing major depressive disorder (MDD) can be exceedingly difficult in a large percentage of patients, but there is some exciting news in that there are newer medications and treatment approaches which may help these patients. These treatments are addressing some of the unmet needs.

Key Points

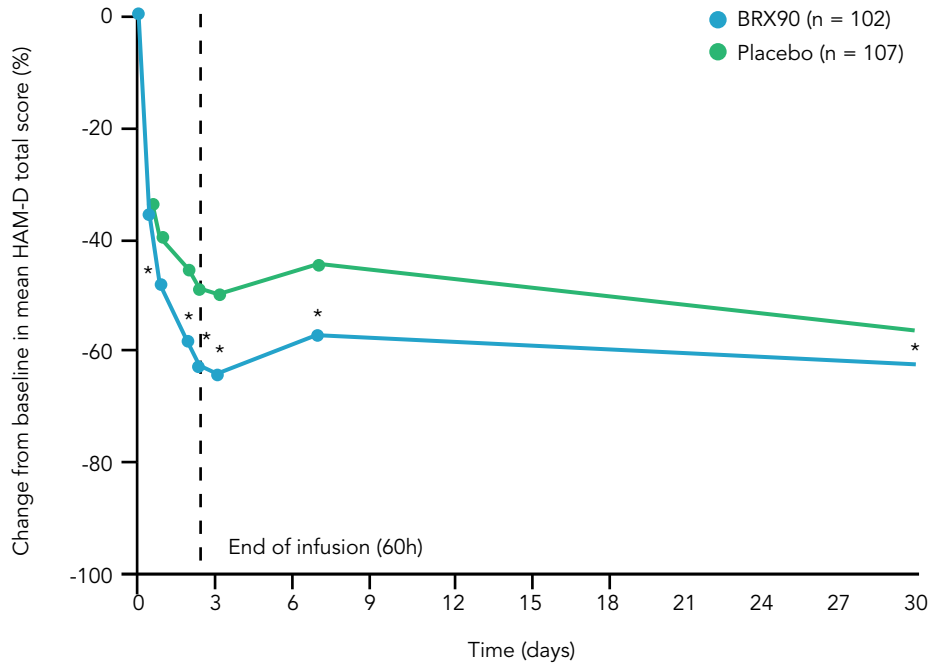
- Disadvantages of the newer treatments are much higher costs than older generic antidepressants and the potential adverse events.
- The newer treatments target some of the unmet needs in improving cognitive deficits that occur with MDD, improving the speed of action onset, and having an indication for treating postpartum depression.
- The risk-benefit ratio of any treatment for depression must be considered and so does the cost-effectiveness.

MOST OF THE OLDER ANTIDEPRESSANTS work by altering levels of monoamines – norepinephrine or serotonin. For example, the selective serotonin reuptake inhibitors (SSRI) work by blocking the reuptake of serotonin into the presynaptic neurons. The newer treatments that have become available work in other areas including hallucinogenic serotonin 2a agonists, glutamatergic transmission, gamma-aminobutyric acid (GABA)-ergic neurosteroids, opioid modulators, or specific brain region or circuit stimulation with devices.

Vortioxetine (Trintellix®) is an antidepressant with an expanded mechanism of action that was FDA approved in 2013. In addition to having serotonin (5HT) reuptake inhibition activity, it is a 5HT1A agonist, a 5HT1b partial agonist, and a 5HT3 and 5HT7 antagonist. Positive trials have been reported in managing severe and non-severe MDD with doses ranging from 10 to 30 mg per day. Most importantly, this agent has been shown to improve cognition in MDD. Vortioxetine has been shown to be superior to duloxetine in improving cognitive function.[1] There are no data to suggest that this agent is a better antidepressant than any of the others, but it does have the pro-cognitive effects, which could be useful for patients. The cognitive effects of the other antidepressants, other than duloxetine, have not been extensively studied. The issue with using this agent is the significant cost (~$400 per month) compared with generic antidepressants which cost less than $25 per month.

Treatment of severe or treatment-resistant depression is another unmet need. Approximately one-third of patients with MDD do not respond to traditional antidepressants. Targeting glutamate is one option that has been investigated. Glutamate interacts with multiple post-synaptic receptors, including the N-methyl-D-aspartate (NMDA) receptor. Ketamine, an anesthetic agent that has been shown to block the NMDA receptor, has been used intravenously to treat chronic pain, depression, post-traumatic stress disorder, and other conditions. The theory of the efficacy of ketamine involves provoking release of glutamate, which then interacts

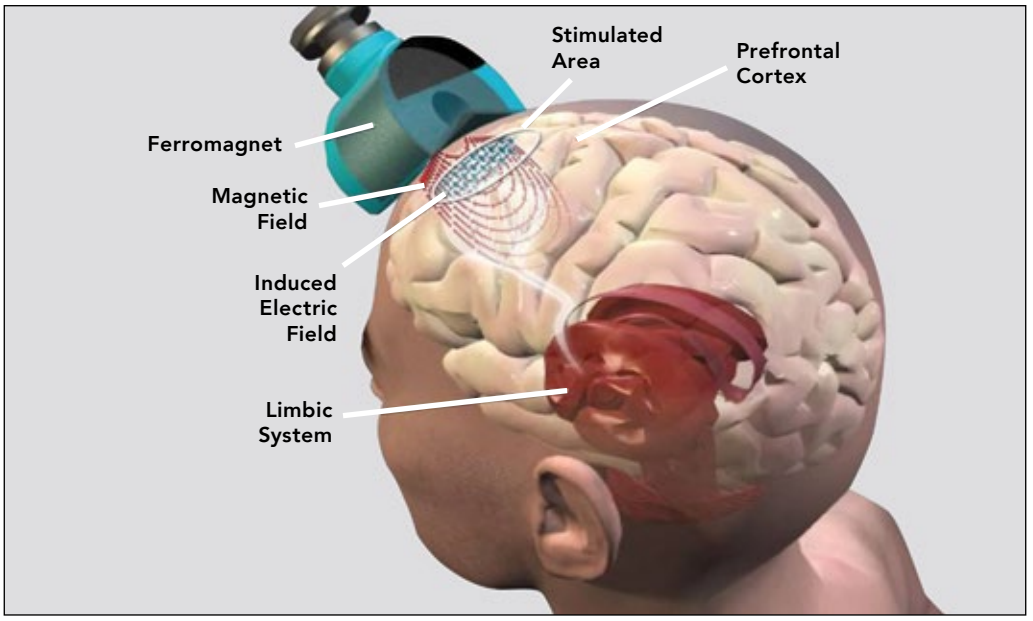
Exhibit 1: Brexanolone 90 mg versus Placebo



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. Many clinicians and researchers think the primary antidepressant effect of ketamine is primarily its opioid effect.[2] Additionally, it is a psychotomimetic that leads to dissociation (i.e., psychedelic trip). Over the course of a week after an infusion, depression scores decline significantly and then begin to increase almost back to baseline.[3] In a National Institute of Mental Health sponsored study, ketamine was compared to midazolam infusions. Because of the psychotomimetic effects of ketamine, an active placebo is required to blind the study.[4] In this trial, the ketamine group had a greater improvement in the Montgomery-Åsberg Depression Rating Scale (MADRS) score than the midazolam group 24 hours after treatment. After adjustment for baseline scores and site, the MADRS score was lower in the ketamine group than in the midazolam group by 7.95 points (95% confidence interval [CI], 3.20 to 12.71). The likelihood of response at 24 hours was greater with ketamine than with midazolam (odds ratio, 2.18; 95% CI, 1.21 to 4.14), with response rates of 64 percent and 28 percent, respectively. In this trial, the MADRS score remained down over the course of a week after infusion with both agents. Because the antidepressant effect wanes over a week after infusion, giving multiple infusions has become the standard for giving ketamine. In a trial of repeat infusions, a series of up to six infusions of ketamine (.5 mg/kg) were administered open-label three times weekly over a 12-day period with an overall response rate (ORR) at study end of 70.8 percent.[5] There was a large mean decrease in MADRS score at two hours after the first ketamine infusion (18.9 $\pm$ 6.6, $p < .001$), and this decrease was largely sustained for the duration of the infusion period. Response at study end was strongly predicted by response at four hours (94% sensitive, 71% specific). Among responders, median time to relapse after the last ketamine infusion was 18 days. Unfortunately, the acute antidepressant efficacy does not appear to be sustained, even with repeated infusions.

To improve the ease of giving ketamine, intranasal administration has been developed. Esketamine (Spravato®) is an intranasal S-isomer of ketamine which is FDA approved, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression in adults. It is a Schedule III controlled substance (CIII) that is given under supervision by a healthcare provider who observes the patient for two hours after the inhalation including blood pressure monitoring. There is

Exhibit 2: Transcranial Magnetic Stimulation



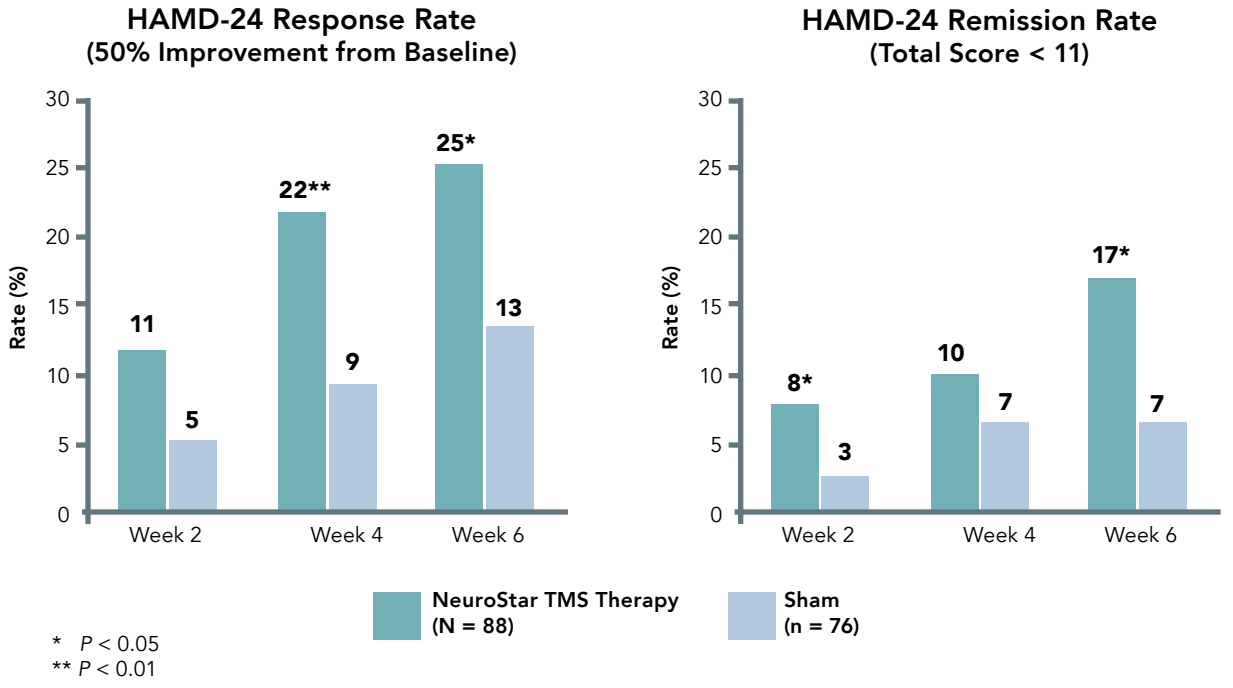
dramatic separation in antidepressant response in the first 24 to 48 hours after a dose, which then begins to decline. In 60 patients with MDD and history of inadequate response to two or more antidepressants, esketamine 28 mg, 56 mg, or 84 mg twice weekly were compared to placebo.[6] The change (least squares mean [SE] difference versus placebo) in the MADRS total score in all three esketamine groups was superior to placebo (esketamine 28 mg: -4.2 [2.09], p = .02; 56 mg: -6.3 [2.07], p = .001; 84 mg: -9.0 [2.13], p < .001), with a significant ascending dose-response relationship (p < .001). Improvement in depressive symptoms appeared to be sustained (-7.2 [1.84]), despite reduced dosing frequency in the open-label phase of this trial.

Combining esketamine and an oral antidepressant together, as a booster at the start of therapy, has been studied. Esketamine nasal spray (56 or 84 mg twice weekly) and an antidepressant was compared to an antidepressant and placebo nasal spray. The change in the MADRS score with esketamine plus antidepressant was significantly greater than with antidepressant plus placebo at day 28 (difference of least square means = -4.0, SE = 1.69, 95% CI = -7.31, -0.64); likewise, clinically meaningful improvement was observed in the esketamine plus antidepressant arm at earlier time points.[7] The five most common adverse events (dissociation, nausea, vertigo, dysgeusia, and dizziness) all were observed more frequently in the esketamine plus antidepressant arm than in the antidepressant plus placebo arm; 7 percent and 0.9 percent of patients in the respective treatment groups discontinued the study drug because of an adverse event. Importantly, during the esketamine studies, there were six deaths of which three were suicides in previously non-suicidal individuals. Monitoring the suicide rate with this agent is important, especially after the patient stops therapy.

Interestingly, intranasal esketamine and intravenous ketamine can be used for rapid reduction of symptoms in patients at imminent risk for suicide.[8,9] With esketamine, significantly greater improvement was observed on the MADRS suicidal thoughts item score at four hours (effect size = 0.67), but not at 24 hours (effect size = 0.35) or at day 25 (effect size = 0.29).[8] Ketamine rapidly reduced suicidal thoughts, within one day and for up to one week in depressed patients with suicidal ideation.[9] Ketamine's effects on suicidal ideation were partially independent of its effects on mood.

Ketamine and esketamine are probably best used acutely to provide rapid reduction of symptoms in those at imminent risk for suicide or in combination with the initiation of antidepressants in those with treatment-resistant depression. Ketamine is

Exhibit 3: Response and Remission Rates in the Indicated Population[11]



* $P < 0.05$
** $P < 0.01$

HAMD = Hamilton Depression Rating Score

approximately $660 to $1,000 per infusion with six infusions, and it is not typically covered by insurance. Esketamine, approximately $700 per 56 mg dose and $1,200 per 84 mg dose, is given twice a week for four weeks, and is then given as maintenance weekly or every other week doses.

Brexanolone (Zulresso®) is an antidepressant approved specifically for postpartum depression, for which there is no other FDA-approved therapy. It is an analogue of allopregnanolone, a progesterone-derived neurosteroid that binds to the GABA receptor, which gives a benzodiazepine like effect. It is hypothesized that brexanolone may exert its effects on anxiety and depression by modulating the hypothalamic-pituitary-adrenal axis, which mediates the body's response to stress through its effect on GABA. This agent is not for outpatient use; it is given as a single intravenous infusion over 60 hours and requires continuous patient monitoring. An oral compound is under investigation. It has been studied in epilepsy, postpartum depression, and refractory depression, but trials in epilepsy failed. In one of the Phase III studies, at the end of the infusion the mean reduction in the Hamilton Depression Rating Scale Score (HAM-D) from baseline was 19.5 points in the brexanolone 60 µg/kg per hour group and 17.7 points (1·2) in the 90 µg/kg per hour group compared with 14.0 points in the placebo group (difference -5.5, p = 0·0013 for the 60 group; -3.7, p = 0·0252 for the 90 group).[10] In the other Phase III study, 90 µg/kg per hour was compared to placebo. The mean reduction in the HAM-D total score from baseline was 14.6 points in the 90 group compared with 12.1 points for the placebo group (difference -2·5 [95% CI -4·5 to -0·5], p = 0·0160).[10] This is a rapidly effective drug (within 3 days) but like ketamine, depression scores increase over a 30-day period after infusion, but do remain lower than baseline (Exhibit 1).[10]

Transcranial magnetic stimulation (TMS) uses a small electromagnetic coil to deliver short, powerful bursts of magnetic energy focused precisely on the left side of the brain's frontal cortex. The TMS magnetic fields are the same type and strength as those produced by a magnetic resonance imaging (MRI) machine. (Exhibit 2). Magnetic fields pass unimpeded through the cranium for 2 to 3 cm in turn inducing an electric current in the brain. This stimulates the firing of nerve cells and the release of neurotransmitters such as 5HT, norepinephrine, and dopamine. The FDA-approved devices deliver a 40-minute treatment once daily for five days per week

for four to six weeks and are indicated for treatment-resistant depression. There is a fairly low response (50% reduction in depression score) and remission rate, but it is better than sham treatment (Exhibit 3).[11] Against a sham treatment, the remission rate is 10 to 11 percent better than placebo.[11,12] Continuing treatment out to six months can improve the clinician and patient rated response to 50 percent or better.[13] TMS is an expensive procedure that costs $12,000 to $15,000 out of pocket; several commercial and government insurance plans are now covering the procedure. The most common adverse event is pain or discomfort at or near the treatment site. These events are transient and typically occur only during the TMS treatment course. There is a rare risk of seizure associated with the use of TMS (< 0.1%).

Modifications to the TMS procedure are being studied to improve the response. The best improvements have been in changing the wave focus and frequency. Accelerated intermittent theta burst stimulation (aiTBS) includes ten sessions of ten minutes with 50 minutes between each session for five days.[14] This protocol delivers 90,000 pulses which is equivalent to a six-week course of traditional TMS. A recent release of open-label results from the Stanford Accelerated Intelligent Neuromodulation Treatment (SAINT) aiTBS paradigm has demonstrated initial efficacy in the treatment of treatment-resistant depression among TMS naïve, TMS non-responders and electroconvulsive therapy (ECT) non-responders; however, post-treatment antidepressant durability (time to relapse) and associated predictors of durability remain unexplored. The SAINT protocol uses resting-state functional connectivity MRI (fcMRI) for precision targeting of the left dorsolateral prefrontal to subgenual anterior cingulate cortex circuit. Nineteen of 21 participants (90.5%) met remission criteria (defined as a score < 11 on the MADRS).[15] Neuropsychological testing demonstrated no negative cognitive adverse events. Double-blinded, sham-controlled trials are needed to confirm the remission rate observed in this initial study. In a difficult to treat population, this remission rate is dramatically better than TMS (31%), ketamine (20.6%), and ECT (48%).[16-18] A randomized controlled trial of aiTBS is ongoing.

A big problem is how to structure payment for TMS treatment, especially given the accelerated protocol. There needs to be a payment structure for per course of treatment rather than individual treatment payment. There also needs to be cost-benefit analyses done for the TMS compared with aiTBS and other treatments. The FDA-approved "dosing" for TMS is likely underdosing.

Conclusion

There are newer treatments for depression, but these have much higher costs than the antidepressants which have been around for a long time and are mostly generic. The newer treatments target some of the unmet needs in improving cognitive deficits that occur with MDD, improving the speed of action onset, having an indication for treating postpartum depression, and providing a good response in treatment-resistant depression. The risk-benefit ratio of any treatment for depression must be considered and so does the cost-effectiveness. Lastly, rationale for payment for these expensive treatments is needed.

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Informed Decision-Making in the Management of Primary Immunodeficiency Diseases: Expert Strategies on Immunoglobulin Replacement Therapy

Richard L. Wasserman, MD, PhD

For a CME/CEU version of this article, please go to
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Summary

Primary immunodeficiency diseases (PIDD) lead to recurrent, chronic, and serious infections because of defects in the immune system. The treatment of PIDD is replacement of missing immunoglobulins, and there are 16 products currently available which can be administered via different avenues and settings.

Key Points

- An individualized biologic threshold for immunoglobulin levels must be established for each patient.
- Immunoglobulin replacement can cause a significant burden of care; this can be reduced by selecting appropriate products and administration routes.
- Several strategies including site of care can be used to manage costs and reduce care-related burden.

PRIMARY IMMUNODEFICIENCY DISEASES (PIDD) are a group of more than 300 diseases with defects in the body's defenses. In most cases, PIDD are associated with acute or recurrent infections, depending on the portion of the immune system affected. Presentation of PIDD varies by whether the specific or innate immune system is involved and the particular deficits present (Exhibit 1). Seventy-eight percent of all PIDD are antibody deficiencies.

When a patient is suspected of having an immune deficiency, the goals of an immunologic evaluation are to prevent premature mortality, minimize physical morbidity, maximize the potential for normal physical and psychosocial growth and development, and define the basis of abnormal infection susceptibility to optimize treatment. Patients should be referred for evaluation when a patient's infection history is outside of the normal range for a clinician's practice and at any age if they have two or more pneumonias clustered in time, bronchiectasis, infection with signal pathogens (*Pneumocystis, Serratia, Pseudomonas*), invasive fungal infection, two or more invasive bacterial infections, disseminated *Neisseria* disease, or recurrent sinusitis after two or more surgeries. Infants with persistent bronchiolitis/interstitial pneumonitis, chronic diarrhea, recurrent or difficult to treat candida or unexplained rash should also be referred. Toddlers and school-aged children should be referred for evaluation if they have persistent otorrhea after myringotomy tube placement, recurrent otitis media after age four, or more than four courses of antibiotics per year. Indicators specifically for adults include recurrent bronchitis in nonsmokers and infections plus autoimmune disorders.

Diagnosis and appropriate treatment are important to improving the quality of life of the patient with PIDD and preventing morbidity and mortality. Before diagnosis, a significant portion of patients have multiple hospitalizations for infections compared with post-diagnosis and treatment. Treatment also reduces the moderate to severe activity limitations

Exhibit 1: Presentations of PIDD

Specific Immune System

- Antibody deficiency syndromes – bacterial infections: respiratory, GI, cutaneous
- Cell-mediated immune defects – severe or persistent viral infections, fungal infections, parasitic infections

Innate Immune System

- Phagocytic cell defects – bacterial and fungal infections
- Complement defects – Neisseria disease, disseminated infection
- Toll-like receptor defects – Staph, pseudomonas
- Signaling pathway defects – bacterial infections

Exhibit 2: First-Line Immunodeficiency Workup

Antibody production defects
- Quantitate Ig isotypes – IgA, IgG, IgM – not IgD
  - IgG subclasses – limited value
  - IgE is helpful
- Measure specific antibody production
  - Protein (diphtheria/tetanus) antigens
  - Carbohydrate (pneumococcal polysaccharide) antigens

Cellular immunity
- Lymphocyte phenotyping
- Proliferation assays

Granulocyte defects
- Dihydrorhodamine

Complement defects
- CH50

Ig = immunoglobulin
CH50 = total complement activity

related to the disease. Patients also miss fewer days of work and/or school with treatment (30 days per year versus 15 days per year).

The components of a first-line immunodeficiency workup are shown in Exhibit 2. There is typically a significant delay in diagnosis of PIDD; in one study, there was at least a five-year delay from the onset of symptoms to the diagnosis.[1]

The primary treatment of PIDD is replacement therapy with immunoglobulin G (IgG). The primary efficacy outcome of all the IgG licensing trials is the rate of acute serious bacterial infections (aSBI). An aSBI is defined as pneumonia, bacteremia, septic arthritis, osteomyelitis, or abscess. There are 16 approved IgG products and studies that show all exceed the standard of less than one aSBI/patient year. Secondary efficacy outcomes examined in the product trials include all infections, days of antibiotic therapy, acute care visits, and days missed from work or school. Although a product may be shown to reduce secondary outcomes, relative efficacy comparisons between products is not possible because of a lack of comparison trials. One cannot say that one product is better than any of the others.

Although the package labeling recommendations for IgG dosing range from 300 mg/kg per month to 800 mg/kg per month based on how studies were done, higher levels of IgG result in lower levels of infections. For every 100 mg/dl the trough level of IgG is increased, the rate of pneumonia is decreased by 27 percent.[2] Because every patient's susceptibility to infections varies, there is a significant body of evidence that dosing should be based on individualized biologic trough levels which prevent infections for a given patient.[2-4] Overall, the correct dose of IgG for a given patient is the dose that keeps the patient well.

IgG replacement can be given by intravenous (IV) or subcutaneous infusion (SC). Exhibit 3 outlines some of the differences between intravenous immunoglobulin (IVIG) infusion, subcutaneous immunoglobulin (SCIG) injection, and the

Exhibit 3: Comparing Routes of IgG Administration

Attribute	IGIV	Conventional IGSC	IGHy
Infusion Frequency	Every 3 to 4 weeks	Daily to every 2 weeks	Every 3 to 4 weeks
Treatment options	Medical supervision Venous access	Self administration No venous access	Self administration or HCP No venous access
Relative Dose	100%	137% of IV	100%
Sites/month	1	2 to 16*	1 to 2
Systemic AEs	Higher than IGSC	Lower than IGIV	Similar to IGSC
Local Aes	Lower than IGSC	Higher than IGIV	Similar to IGSC

*Depends on concentration of product and total dose required
IGIV = intravenous immunoglobulin; IGSC = subcutaneous immunoglobulin;
IGHy = hyaluronidase facilitated subcutaneous immunoglobulin; HCP = health care provider

newest type of product, hyaluronidase facilitated subcutaneous infusion (IGHy).

One issue with IgG is that the FDA uses area under the time/concentration curve (AUC) derived from small molecule pharmacokinetics to evaluate comparability of a new product to already approved products and IVIG to SCIG products. New products must demonstrate AUC similar to already licensed products, and the FDA mandates SC dosing to achieve AUC comparable to IV. There are no data to support this as an appropriate comparison. Bioavailability of subcutaneous IgG (SCIG) is approximately 63 percent of intravenous IgG (IVIG) and, thus, the FDA-approved package labeling recommends a 1.4 dose adjustment factor when converting to SCIG from IVIG; the European Union approval of IgG products does not have a similar recommendation. Many immunologists do not apply the adjustment factor. If a patient is on a high dose of IVIG, the conversion to SCIG can be made on a mg/kg basis with no adjustment; patients on lower doses of IVIG doses (~300 mg/kg) may require the dose adjustment. Most prescriptions of IgG for PIDD are done by non-immunologists, so there may be overdosing of SCIG for many patients based on package labeling recommendations. Specialty pharmacy dosing decisions based on physician order to treat based on package labeling typically adheres to using the adjustment factor, but not all patients may need the higher SC dose. It should be noted that IGHy dosing is a one-to-one conversion to IVIG.

Home-based administration of SCIG/IGHy replacement results in the best quality of life compared with hospital, infusion center administration or home IVIG by a nurse.[5,6] Approximately 94 percent of SC products are self-infused at home. Other advantages of the SC route are less time to complete administration, fewer systemic adverse events, and less time away from work and/or school for infusion compared to the IV route. Patients receiving IgG report missing a significant number of days of work or school because of administration requirements or adverse events, and anything which can reduce these can improve quality of life and reduce the burden of care. Between 2013 and 2018, SC administration increased from 25 percent to 34 percent of total patients, and clinic infusions continued to account for 39 percent of total patients.[7] The percentage of patients receiving SC products at home continues to increase but varies by practice; more than 60 percent of our patients currently self-infused SC products at home.

Tolerability of IgG replacement varies among patients because of administration-related adverse events and can impact product selection. SCIG and IGHy result in lower rates of these adverse events compared with IVIG. These reactions are thought to be related to high peak levels of IgG and/or chronic bacterial colonization. The most common administration-related adverse events are migraine

headache, myalgias, malaise, and fatigue. Less common reactions include fever, diarrhea, rash, cough, chest tightness, and sinus tenderness. Reactions are more frequent on the first or second infusion, or after a hiatus in treatment. Switching around among products can result in these reactions occurring. Reactions may also be related to the infusion rate and can be decreased by reducing the rate.

Serious, life-threatening events can occur with IgG replacement. Renal failure can be caused by carbohydrate containing products, particularly sucrose. Risk factors for renal failure include older age, renal compromise, and diabetes. Thrombosis caused by activated factor 11a contamination can also occur, but this risk has been reduced by better filtration of products. Risks for this adverse event include older age, previous thrombotic events, thrombophilia, and hyperviscosity. Aseptic meningitis can occur in those with a history of migraine. Transfusion-related acute lung injury is a rare serious adverse event with no known risk factors. Product-related differences are decreasing because of better production, screening, and filtration procedures.

Patient surveys by the Immune Deficiency Foundation have found that 87 to 90 percent of patients report having had an adverse event of some type with IgG. Aseptic meningitis was the most reported serious adverse event, followed by blurred vision and thrombosis. Patients reported that serious adverse events occurred primarily when using a new product for the first time.

Minimizing the risks of severe adverse events also impacts product selection. Some examples of product selection to minimize severe reactions are given here. Those who are over 55, have diabetes, or have renal disease should not receive carbohydrate containing products. Those with a thrombosis history should receive limited doses per infusion and lower infusion rates. Sodium containing products should be avoided in those with cardiac disease. In addition to sodium free products, those with compensated heart failure should receive more concentrated products (10% or 20% instead of 5% IVIG) to minimize the fluid volume given. Hemodynamically unstable neonates should also receive more concentrated formulations. For those with poorly controlled migraine, subcutaneous administration is preferred; however, if IV must be used, 50 percent of the total dose and pre-treatment with a triptan can be done with the first administration.

The cost of IgG products is an issue for managed care. In 2018, IgG products comprised 8 percent of medical pharmacy spend for commercial plans.[8] Between 2015 and 2016, spending on this category increased to 16 percent. It should be noted that only 23 percent of IgG use is for PIDD.[9]

Because of the high costs, managed care has sought various strategies to manage these costs. Changing to home infusion instead of a hospital or infusion center is one cost-saving measure. A 12-month prospective study of Canadian PIDD patients receiving SCIG at home versus IVIG in the hospital found that nondrug costs ($1,836 versus $4,187) and physician costs ($84 versus $744) were lower.[10] Home IVIG treatment is also associated with fewer episodes of bronchitis and pneumonia.[11] Most managed care plans have a site of care strategy for IgG adminsitration.[12] Among plans with one, 89 percent include IVIG. The most expensive place to administer these products is inpatient at an academic medical center, followed by outpatient at an academic medical center. If the product must be given under medical supervision, non-academic hospitals are less costly.

Although many managed care plans use various strategies to contain costs of IgG, management can increase global costs. Rigid referred drug lists ignore IgG tolerability data and step therapy requirements penalize patients. Failing with a product means experiencing unacceptable adverse events which can last for several days after an infusion, impact quality of life, and require other therapies to treat, which also have a cost. Many PIDD patients miss more work or school because of IgG adverse events than they do from infections.[13] Postponed treatment because of managed care requirements and reimbursement hurdles places the patient at risk of infection and hospitalization.

Optimization of care is going to be the most cost-effective approach, with better adherence, fewer infections, and fewer adverse events. There are a few recommendations for managed care to implement to improve care of the PIDD patients. Practicing immunologists are best able to individualize care and thus should be caring for these patients. Managed care should encourage non-academic experts to care for PIDD patients because care in academic centers is more costly. They should also encourage the use of SCIG or IGHy over IVIG and home or office based IVIG infusion over infusion centers and hospitals. Managed care could create IgG prescribing pre-checks or pre-authorization for experienced, reliable physicians to reduce both provider and patient burden. Rigid step care approaches that limit dosing or require failure of several products should not be used.

Conclusion

Understanding the disease burden of PIDD as well as the burden of care should inform managed

care decision-making about IgG products. Immunoglobulin replacement can cause a significant burden of care; this can be reduced by selecting appropriate products and administration route. The best patient outcome can be achieved by allowing clinicians to choose the best product, setting, and dosing regimen for a given patient and this is often the least costly option.

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Notes

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