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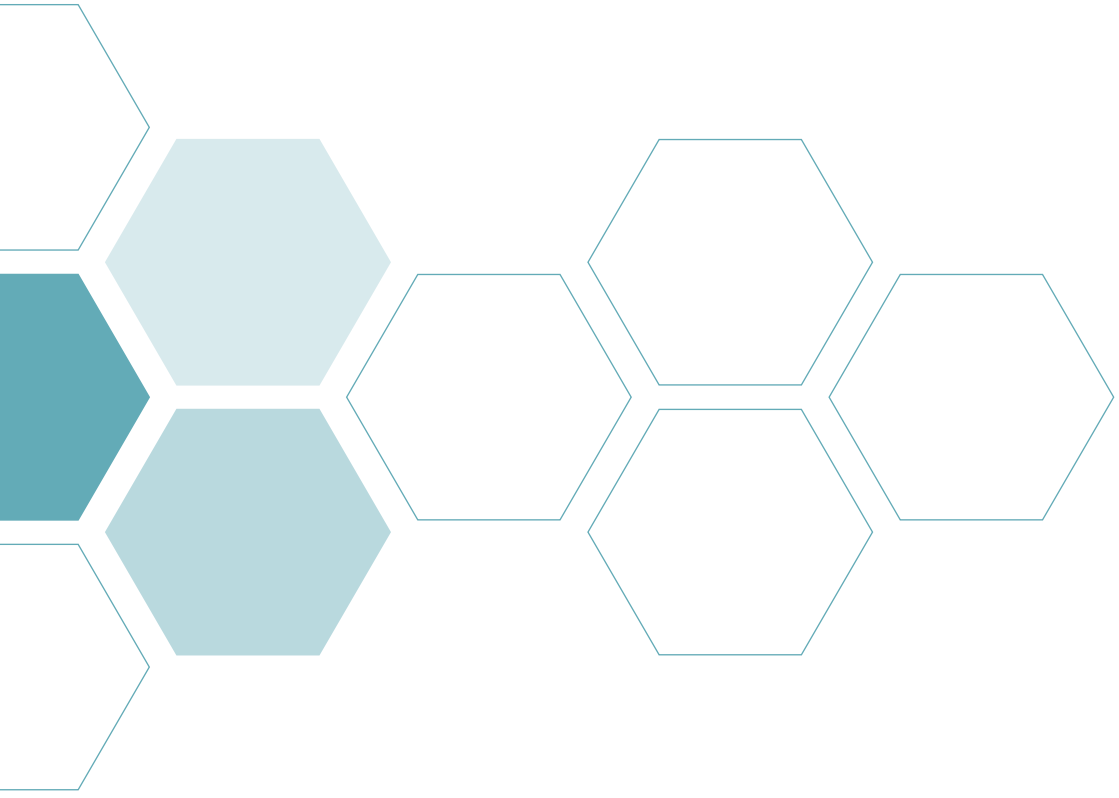
Educating Medical Directors of Employers, Health Plans and Provider Systems



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Vol. 26, No. 2, 2023

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FOR ADULTS WITH SCHIZOPHRENIA OR BIPOLAR I OR II DISORDER,

LET'S FIND COMMON GROUND IN THE TREATMENT OF AGITATION

Not an actual patient or healthcare provider.

IGALMI is a sublingual film purposefully designed to support a cooperative approach to agitation intervention[1,2]

INDICATION

IGALMI is indicated for the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults. **Limitations of Use: The safety and effectiveness of IGALMI have not been established beyond 24 hours from the first dose.**

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hypotension, Orthostatic Hypotension, and Bradycardia: IGALMI causes dose-dependent hypotension, orthostatic hypotension, and bradycardia. In clinical studies with IGALMI, patients were excluded if they had treatment with alpha-1 noradrenergic blockers, benzodiazepines, other hypnotics or antipsychotic drugs four hours prior to study drug administration; had a history of syncope or syncopal attacks; SBP < 110 mmHg; DBP < 70 mmHg; HR < 55 beats per minute; or had evidence of hypovolemia or orthostatic hypotension. Because IGALMI decreases sympathetic nervous system activity, hypotension and/or bradycardia may be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension, and in geriatric patients. Avoid use of IGALMI in patients with hypotension, orthostatic hypotension, advanced heart block, severe ventricular dysfunction, or history of syncope. After IGALMI administration, patients should be adequately hydrated and should sit or lie down until vital signs are within normal range. If a patient is unable to remain seated or lying down, precautions should be taken to reduce the risk of falls. Ensure that a patient is alert and not experiencing orthostatic hypotension or symptomatic hypotension prior to allowing them to resume ambulation.

QT Interval Prolongation: IGALMI prolongs the QT interval. Avoid use of IGALMI in patients at risk of torsades de pointes or sudden death, including those with known QT prolongation, a history of other arrhythmias, symptomatic bradycardia, hypokalemia, or hypomagnesemia, and in patients receiving other drugs known to prolong the QT interval.

Somnolence: IGALMI can cause somnolence. Patients should not perform activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery, for at least eight hours after taking IGALMI.

Risk of Withdrawal Reactions, Tolerance, and Tachyphylaxis: IGALMI was not studied for longer than 24 hours after the first dose. There may be a risk of physical dependence, a withdrawal syndrome, tolerance, and/or tachyphylaxis if IGALMI is used in a manner other than indicated.

IGALMI IS THE FIRST AND ONLY SUBLINGUAL FILM FORMULATION OF DEXMEDETOMIDINE

Igalmi™
(dexmedetomidine)
sublingual film · 120 mcg, 180 mcg

- **TARGETS** a key mediator of agitation[1,3,4]*
- **NONINVASIVE** sublingual film with a mucoadhesive design, so it cannot be spit out[1,4]
- **PATIENT ADMINISTERED** under the supervision of a healthcare provider[1]

Learn more about the proven reduction in agitation related to schizophrenia and bipolar I or II disorder at IGALMIhcp.com

*IGALMI reduces the release of norepinephrine, a key mediator among other neurotransmitters thought to be involved in agitation.[1,3,4]

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were somnolence, oral paresthesia or oral hypoesthesia, dizziness, dry mouth, hypotension, and orthostatic hypotension.

DRUG INTERACTIONS

Drugs That Prolong the QT Interval: Avoid use. Concomitant use of drugs that prolong the QT interval may add to the QT-prolonging effects of IGALMI and increase the risk of cardiac arrhythmia.

Anesthetics, Sedatives, Hypnotics, and Opioids: Concomitant use may cause enhanced CNS-depressant effects. Reduction in dosage of IGALMI or the concomitant medication should be considered.

USE IN SPECIFIC POPULATIONS

Hepatic Impairment and Geriatric Patients (≥65 years old): A lower dose is recommended in patients with hepatic impairment and geriatric patients. See the full Prescribing Information for the recommended dosage depending on the agitation severity.

Please see the Brief Summary of the full Prescribing Information on the following pages.

To report SUSPECTED ADVERSE REACTIONS, contact BioXcel Therapeutics, Inc. at 1-833-201-1088 or medinfo@bioxceltherapeutics.com, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

References: 1. IGALMI. Package insert. BioXcel Therapeutics, Inc.; 2022. **2.** Wilson MP, et al. *West J Emerg Med*. 2012;13(1):26-34. doi:10.5811/westjem.2011.9.6866 **3.** Miller CWT, et al. *West J Emerg Med*. 2020;21(4):841-848. doi:10.5811/westjem.2020.4.45779 **4.** Data on file. BXCL501-301 CSR (SERENITY I). BioXcel Therapeutics, Inc.; January 2021.

bioxcel therapeutics®

Igalmi™
(dexmedetomidine)
sublingual film · 120 mcg,180 mcg

IGALMI™ (dexmedetomidine) sublingual film, for sublingual or buccal use. Rx Only. Brief Summary of Prescribing Information (PI) for IGALMI. See full PI.

Indication: IGALMI is indicated for the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults. Limitations of Use: The safety and effectiveness of IGALMI have not been established beyond 24 hours from the first dose.

Important Recommendations Prior to Initiating IGALMI and During Therapy: IGALMI should be administered under the supervision of a healthcare provider. A healthcare provider should monitor vital signs and alertness after IGALMI administration to prevent falls and syncope.

IGALMI is for sublingual or buccal administration. Do not chew or swallow IGALMI. Do not eat or drink for at least 15 minutes after sublingual administration, or at least one hour after buccal administration.

Recommended Dosage: The initial dose of IGALMI is based on agitation severity, with lower doses recommended in patients with hepatic impairment and geriatric patients. If agitation persists after the initial dose, up to two additional doses may be administered at least two hours apart, depending upon the patient population and agitation severity. Assess vital signs including orthostatic measurements prior to the administration of any subsequent doses. Due to risk of hypotension, additional half-doses are not recommended in patients with systolic blood pressure (SBP) less than 90 mmHg, diastolic blood pressure (DBP) less than 60 mmHg, heart rate (HR) less than 60 beats per minute, or postural decrease in SBP ≥ 20 mmHg or in DBP ≥ 10 mmHg.

The recommended dose in adults is 120 mcg for mild or moderate agitation and 180 mcg for severe agitation. Patients with mild or moderate hepatic impairment and mild to moderate agitation should receive 90 mcg. Patients with mild or moderate hepatic impairment and severe agitation should receive 120 mcg. Patients with severe hepatic impairment and mild to moderate agitation should receive 60 mcg. Patients with severe hepatic impairment and severe agitation should receive 90 mcg. Geriatric patients (patients ≥65 years old) with mild, moderate or severe agitation should receive 120 mcg. See Full Prescribing Information for recommendations on administering up to two additional doses and maximum recommended dosages.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS

Hypotension, Orthostatic Hypotension, and Bradycardia: IGALMI causes dose-dependent hypotension, orthostatic hypotension, and bradycardia. In clinical studies, 18%, 16%, and 9% of patients treated with 180 mcg of IGALMI, 120 mcg of IGALMI, and placebo, respectively, experienced orthostatic hypotension (defined as SBP decrease ≥ 20 mmHg or DBP decrease ≥ 10 mmHg after 1, 3, or 5 minutes of standing) at 2 hours post-dose. In those studies, 7%, 6%, and 1% of patients treated with 180 mcg of IGALMI, 120 mcg of IGALMI, and placebo, respectively, experienced HR ≤ 50 beats per minute within 2 hours of dosing. In clinical studies with IGALMI, patients were excluded if they had treatment with alpha-1 noradrenergic blockers, benzodiazepines, other hypnotics or antipsychotic drugs four hours prior to study drug administration; had a history of syncope or syncopal attacks; SBP < 110 mmHg; DBP < 70 mmHg; HR < 55 beats per minute; or had evidence of hypovolemia or orthostatic hypotension.

Reports of hypotension and bradycardia, including some resulting in fatalities, have been associated with the use of another dexmedetomidine product given intravenously (IGALMI is for sublingual or buccal use and is not approved for intravenous use). Clinically significant episodes of bradycardia and sinus arrest have been reported after administration of this other dexmedetomidine product to young, healthy adult volunteers with high vagal tone and when this product was given by rapid intravenous or bolus administration.

Because IGALMI decreases sympathetic nervous system activity, hypotension and/or bradycardia may be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension, and in geriatric patients. Avoid use of IGALMI in patients with hypotension, orthostatic hypotension, advanced heart block, severe ventricular dysfunction, or history of syncope. After IGALMI administration, patients should be adequately hydrated and should sit or lie down until vital signs are within normal range. If a patient is unable to remain seated or lying down, precautions should be taken to reduce the risk of falls. Ensure that a patient is alert and not experiencing orthostatic hypotension or symptomatic hypotension prior to allowing them to resume ambulation.

QT Interval Prolongation: IGALMI prolongs the QT interval. Avoid use of IGALMI in patients at risk of torsades de pointes or sudden death including those with known QT prolongation, a history of other arrhythmias, symptomatic bradycardia, hypokalemia or hypomagnesemia, and in patients receiving other drugs known to prolong the QT interval.

Somnolence: IGALMI can cause somnolence. In placebo-controlled clinical studies in adults with agitation associated with schizophrenia or bipolar I or II disorder, somnolence (including fatigue and sluggishness) was reported in 23% and 22% of patients treated with IGALMI 180 mcg and 120 mcg, respectively, compared to 6% of placebo-treated patients. Patients should not perform activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery, for at least eight hours after taking IGALMI.

Risk of Withdrawal Reactions: Symptoms of withdrawal have been observed after procedural sedation with another dexmedetomidine product administered intravenously. In this study, 12 (5%) adult patients who received intravenous dexmedetomidine up to 7 days (regardless of dose) experienced at least 1 event related to withdrawal within the first 24 hours after discontinuing dexmedetomidine and 7 (3%) adult patients who received intravenous dexmedetomidine experienced at least 1 event related with withdrawal 24 to 48 hours after discontinuing dexmedetomidine. The most common withdrawal reactions were nausea, vomiting, and agitation. In these subjects, tachycardia and hypertension requiring intervention occurred at a frequency of <5% in the 48 hours following intravenous dexmedetomidine discontinuation. IGALMI was not studied for longer than 24 hours after the first dose. There may be a risk of physical dependence and a withdrawal syndrome if IGALMI is used in a manner other than indicated.

Tolerance and Tachyphylaxis: Use of another dexmedetomidine product administered intravenously beyond 24 hours has been associated with tolerance and tachyphylaxis and a dose-related increase in adverse reactions. IGALMI was not studied for longer than 24 hours after the first dose. There may be a risk of tolerance and tachyphylaxis if IGALMI is used in a manner other than indicated.

ADVERSE REACTIONS, Clinical Studies Experience: Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

The safety of IGALMI was evaluated in 507 adult patients with agitation associated with schizophrenia (N=255) or bipolar I or II disorder (N=252) in two randomized, placebo-controlled studies (Studies 1 and 2). In both studies, patients were admitted to a clinical research unit or a hospital and remained under medical supervision for at least 24 hours following treatment. Patients were 18 to 71 years of age (mean age was 46 years old); 45% were female and 55% were male; 66% were Black, 31% were White, 2% were multiracial, and 1% were other.

In these studies, patients received an initial dose of IGALMI 180 mcg (N=252), IGALMI 120 mcg (N=255), or placebo (N=252). Patients who were hemodynamically stable (i.e., those with systolic blood pressure (SBP) > 90 mmHg, diastolic blood pressure (DBP) > 60 mmHg, and heart rate (HR) > 60 beats per minute) and without orthostatic hypotension (i.e., reduction in SBP < 20 mmHg or DBP < 10 mmHg upon standing) were eligible for an additional dose after 2 hours. An additional half dose (90 mcg, 60 mcg, or placebo) was given to 7.1% (18/252), 22.7% (58/255) and 44.0% (111/252) of patients in the IGALMI 180 mcg, IGALMI 120 mcg or placebo arms, respectively. After at least an additional 2 hours, an additional second half dose (total IGALMI dose of 360 mcg, total IGALMI dose of 240 mcg, or placebo, respectively) was given to 3.2% (8/252), 9.4% (24/255), and 21.0% (53/252) of patients in the IGALMI 180 mcg, IGALMI 120 mcg or placebo arms, respectively.

In these studies, one patient discontinued treatment due to an adverse reaction of oropharyngeal pain.

The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) were: somnolence, oral paresthesia or oral hypoesthesia, dizziness, dry mouth, hypotension, and orthostatic hypotension.

Adverse reactions that occurred in IGALMI-treated patients at a rate of at least 2% and at a higher rate than in placebo-treated patients in Studies 1 and 2 were as follows (adverse reaction is followed by percentage of patients treated with IGALMI 180 mcg (n = 252), IGALMI 120 mcg (n = 255) and placebo (n = 252): Somnolence, includes the terms fatigue and sluggishness, (23%, 22%, 6%); Oral paresthesia or oral hypoesthesia (7%, 6%, 1%); Dizziness (6%, 4%, 1%); Hypotension (5%, 5%, 0%); Orthostatic hypotension (5%, 3%, <1%); Dry Mouth (4%, 7%, 1%); Nausea (3%, 2%, 2%); Bradycardia (2%, 2%, 0%); Abdominal discomfort, including dyspepsia, gastroesophageal reflux disease (2%, 0%, 1%).

Hypotension, Orthostatic Hypotension, and Bradycardia in Two Placebo-Controlled Studies: In clinical studies, patients were excluded if they were treated with alpha-1 noradrenergic blockers, benzodiazepines, antipsychotic drugs, or other hypnotics four hours prior to study drug administration; had a history of syncope or syncopal attacks; their SBP was less than 110 mmHg; their DBP was less than 70 mmHg; their HR was less than 55 beats per minute; or they had evidence of hypovolemia or orthostatic hypotension. In these studies, vital signs were monitored (at 30 minutes, 1-, 2-, 4-, 6-, and 8- hours post-dose), including orthostatic vital signs at 2-, 4-, and 8-hours post-dose. Maximum positional decreases in SBP and DBP after standing were observed at two hours post-dose. Maximal reductions on BP and HR were observed two hours post-dose.

The mean BP (in mmHg) and HR decrease (in bpm) across all patients from both studies at 2 hours post-dose were as follows for patients treated with IGALMI 180 mcg (n = 252), IGALMI 120 mcg (n = 255) and placebo (n = 252): Mean SBP Decrease (15, 13, 1), Mean DBP Decrease (mmHg) (8, 7, <1), Mean Heart Rate Decrease (9, 7, 3). In the clinical studies: 13%, 8%, and <1% of patients in the single dose 180 mcg IGALMI, 120 mcg IGALMI, and placebo groups, respectively, experienced SBP ≤ 90 mmHg and a decrease ≥ 20 mmHg of SBP within 24 hours of dosing; 19%, 17%, and 2% of the patients in the 180 mcg IGALMI, 120 mcg IGALMI, and placebo groups, respectively, had a DBP ≤ 60 mmHg and a DBP decrease ≥ 10 mmHg within 24 hours of dosing; 4%, 3%, and 0% of patients in the 180 mcg IGALMI, 120 mcg IGALMI, and placebo groups, respectively, had a HR ≤ 50 beats per minute and a HR decrease ≥ 20 beats per minute within 24 hours of dosing.

At 8 hours post-dose, 2% of patients in the IGALMI 180 mcg group experienced a SBP ≤ 90 mmHg and decrease ≥ 20 mmHg compared with one patient (<1%) in the IGALMI 120 mcg group and none in the placebo group. At 24 hours, none of the patients in the IGALMI 180 mcg group experienced a SBP ≤90 mmHg and decrease ≥ 20 mmHg compared with one patient (<1%) in the IGALMI 120 mcg group and none in the placebo group. At 8 hours post-dose, none of the patients in the IGALMI 180 mcg group had a HR ≤ 50 beats per minute and a HR decrease ≥ 20 beats per minute compared with one patient in the 120 mcg group (<1%) and none in the placebo group.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of another dexmedetomidine product given intravenously (IGALMI is not approved for intravenous use). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Anemia; *Cardiac Disorders:* Arrhythmia, atrial fibrillation, atrioventricular block, bradycardia, cardiac arrest, cardiac disorder, extrasystoles, myocardial infarction, supraventricular tachycardia, tachycardia, ventricular arrhythmia, ventricular tachycardia; *Eye Disorders:* Photopsia, visual impairment; *Gastrointestinal Disorders:* Abdominal pain, diarrhea, nausea, vomiting; *General Disorders and Administration Site Conditions:* Chills, hyperpyrexia, pain, pyrexia, thirst; Hepatobiliary Disorders: Hepatic function abnormal, hyperbilirubinemia; Investigations: Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood urea increased, electrocardiogram T wave inversion, gammaglutamyltransferase increased, electrocardiogram QT prolonged; *Metabolism and Nutrition Disorders:* Acidosis, hyperkalemia, hypoglycemia, hypovolemia, hypernatremia; *Nervous System Disorders:* Convulsion, dizziness, headache, neuralgia, neuritis, speech disorder; *Psychiatric Disorders:* Agitation, confusional state, delirium, hallucination, illusion; *Renal and Urinary Disorders:* Oliguria, polyuria; *Respiratory, Thoracic and Mediastinal Disorders:* Apnea, bronchospasm, dyspnea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion, respiratory acidosis; *Skin and Subcutaneous Tissue Disorders:* Hyperhidrosis, pruritus, rash, urticaria; *Surgical and Medical Procedures:* Light anesthesia;

Vascular Disorders: Blood pressure fluctuation, hemorrhage, hypertension, hypotension

DRUG INTERACTIONS

Drugs that Prolong the QT Interval: Concomitant use of drugs that prolong the QT interval may add to the QT-prolonging effects of IGALMI and increase the risk of cardiac arrhythmia. Avoid the use of IGALMI in combination with other drugs known to prolong the QT interval.

Anesthetics, Sedatives, Hypnotics, and Opioids: Concomitant use of IGALMI with anesthetics, sedatives, hypnotics, or opioids is likely to lead to enhanced CNS depressant effects. Specific studies with another dexmedetomidine product given intravenously have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. Due to possible enhanced CNS effects when given concomitantly with IGALMI, consider a reduction in dosage of IGALMI or the concomitant anesthetic, sedative, hypnotic, or opioid.

USE IN SPECIFIC POPULATIONS

Pregnancy, Risk Summary: There are no available data on IGALMI use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal effects. Available data from published randomized controlled trials and case reports over several decades of use with intravenously administered dexmedetomidine during pregnancy have not identified a drug-associated risk of major birth defects or miscarriage; however, the reported exposures occurred after the first trimester. Most of the available data are based on studies with exposures that occurred at the time of cesarean-section delivery, and these studies have not identified an adverse effect on maternal outcomes or infant Apgar scores. Available data indicate that dexmedetomidine crosses the placenta.

In animal reproductive studies fetal toxicity occurred in the presence of maternal toxicity with subcutaneous administration of dexmedetomidine to pregnant rats during organogenesis at doses 5 times the maximum recommended human dose [MRHD] of 360 mcg/day based on mg/m^2 body surface area. Adverse developmental effects, including early implantation loss and decreased viability of second generation offspring, occurred when pregnant rats were subcutaneously administered doses less than or equal to the MRHD based on mg/m^2 from late pregnancy through lactation and weaning *(see Data)*.

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

Data: *Animal Data*: Increased post-implantation losses and reduced live pups in the presence of maternal toxicity (decreased body weight) occurred in a rat embryo-fetal development study in which pregnant dams were administered subcutaneous doses of dexmedetomidine of 200 mcg/kg/day (equivalent to 5 times the MRHD of 360 mcg/day based on mg/m^2) during the period of organogenesis (Gestation Day (GD) 5 to 16). No embryo-fetal toxicity was observed at 20 mcg/kg/day (less than the MRHD of 360 mcg/day based on mg/m^2). No malformations were reported at any dose level.

No malformation or embryo-fetal toxicity were observed in a rabbit embryo-fetal developmental study in which pregnant dams were administered dexmedetomidine intravenously at doses up to 96 mcg/kg/day (equivalent to 5 times the MRHD of 360 mcg/day based on mg/m^2) during the period of organogenesis (GD 6 to 18).

Reduced pup and adult offspring weights and grip strength were reported in a rat developmental toxicology study in which pregnant females were administered dexmedetomidine subcutaneously at 8 mcg/kg/day (less than the MRHD of 360 mcg/day based on mg/m^2) during late pregnancy through lactation and weaning (GD 16 to postnatal day [PND] 25). Decreased viability of second generation offspring and an increase in early implantation loss along with delayed motor development occurred at 32 mcg/kg/day (equivalent to the MRHD of 360 mcg/day based on mg/m^2) when first generation offspring were mated. This study limited dosing to hard palate closure (GD 15-18) through weaning instead of standard dosing from implantation (GD 6-7) to weaning (PND 21).

Lactation, *Risk Summary*: Available published literature report the presence of dexmedetomidine in human milk following intravenous administration. There is no information regarding the effects of dexmedetomidine on the breastfed child or the effects on milk production. Advise women to monitor the breastfed infant for irritability. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IGALMI and any potential adverse effects on the breastfed child from IGALMI or from the underlying maternal condition.

Pediatric Use: The safety and effectiveness of IGALMI have not been established in pediatric patients.

Geriatric Use: Fifteen geriatric patients (≥ 65 years of age) were enrolled (no patients were 75 years of age and older) in the clinical studies for acute treatment of agitation associated with schizophrenia or bipolar I or II disorder. Of the total number of IGALMI-treated patients in these clinical studies, 11/507 (2.2%) were 65 years of age and older. Dosage reduction of IGALMI is recommended in geriatric patients. A higher incidence of bradycardia and hypotension was observed in geriatric patients compared to younger adult patients after intravenous administration of another dexmedetomidine product. The pharmacokinetic profile of intravenous dexmedetomidine was not altered in geriatric subjects. Clinical studies of IGALMI did not include sufficient numbers of patients 65 years of age and older to determine whether there were differences in the effectiveness of IGALMI in the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder compared to younger adult patients.

Hepatic Impairment: Dexmedetomidine clearance was decreased in patients with hepatic impairment (Child-Pugh Class A, B, or C). Thus, a dosage reduction of IGALMI is recommended in patients with hepatic impairment compared to patients with normal hepatic function.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: IGALMI contains dexmedetomidine, which is not a controlled substance.

Dependence, Physical Dependence: Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. The dependence potential of dexmedetomidine has not been studied in humans. However, because studies in rodents and primates have demonstrated that intravenous dexmedetomidine exhibits pharmacologic actions similar to those of clonidine, it is possible that dexmedetomidine may produce a clonidine-like withdrawal syndrome upon abrupt discontinuation. IGALMI was not studied for longer than 24 hours after the first dose. There may be risk of physical dependence and a withdrawal syndrome if IGALMI is used in a manner other than indicated.

Tolerance: Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). IGALMI has not been studied for longer than 24 hours after the first dose. There may be a risk for tolerance if IGALMI is administered in a manner other than indicated.

OVERDOSAGE: In a tolerability study of intravenous dexmedetomidine in which healthy adult subjects were administered doses at and above the recommended dose of 0.2 to 0.7 mcg/kg/hour, the maximum blood concentration was approximately 13 times the upper boundary of the therapeutic range for the intravenous dexmedetomidine (IGALMI is not approved for intravenous use). The most notable effects observed in two subjects who achieved the highest doses were first degree atrioventricular block and second-degree heart block.

Five adult patients received an overdose of intravenous dexmedetomidine in intensive care unit sedation studies. Two patients who received a 2 mcg/kg loading dose (twice the recommended loading dose) over 10 minutes, experienced bradycardia and/or hypotension. One patient who received a loading intravenous bolus dose of undiluted dexmedetomidine (19.4 mcg/kg), had cardiac arrest from which he was successfully resuscitated.

Consider contacting a Poison Center (1-800-222-1222) or a medical toxicologist for overdosage management recommendations for IGALMI.

Distributed by: BioXcel Therapeutics, Inc., 555 Long Wharf Drive 12th Floor New Haven, CT 06511

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New Developments in the Treatment and Management of Heart Failure: Managed Care Considerations on the Evolving Paradigm in HFrEF and HFpEF

Alanna A. Morris, MD, MSc

This journal article is supported by educational grants from Merck Sharp & Dohme LLC; Novartis Pharmaceuticals Corporation.

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 heart failure has undergone significant changes over the past few years. A four-pillar medication strategy is now recommended and this strategy includes two newer classes of medications which have been shown to improve morbidity, mortality, and hospitalization rates.

Key Points

- ARNI + beta-blocker + MRA + SGLT2i is the new standard of care for heart failure with reduced ejection fraction (HFrEF).
- There are demonstrated benefits of (ARNI) and (SGLT2i) across the spectrum of EF below normal, which includes a subset of those with preserved ejection fraction (HFpEF).
- Morbidity, mortality, and hospitalizations can be reduced with a multidisciplinary and comprehensive disease management program.

HEART FAILURE (HF) CAUSES SIGNIFICANT morbidity, mortality, and increased costs in the United States (U.S.). A major cost-driver is the high incidence of hospitalizations. There are about 6.5 million people in the U.S. with HF which results in over a million hospitalizations annually.[1] Mortality from HF is 46 percent at five years after diagnosis and the overall cost in the U.S. has been estimated at $30.7 billion.

HF is a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion.[2] HF is classified by ejection fraction (EF) (Exhibit 1).[2] The primary focus of the treatment portion of this article is HF with reduced ejection fraction (HFrEF). Staging of HF has been updated and now includes stages A to D. Exhibit 2 shows the stages with the focus here on Stage C (i.e., patients with current or past symptomatic HF).[2]

In addition to history, signs and symptoms, electrocardiogram and echocardiography, certain biomarkers are recommended for HF diagnosis. The natriuretic peptide system impacts salt and water handling, pressure regulation and influences myocardial structure and function. B-type natriuretic peptide (BNP) is a natriuretic hormone initially identified in the brain but released primarily from the heart, particularly the ventricles. Cleavage of the prohormone proBNP produces biologically active 32 amino acid BNP as well as biologically inert 76 amino acid N-terminal pro-BNP (NT-proBNP). Exhibit 3 shows the American

Exhibit 1: Classifications of HF According to Ejection Fraction (EF)[2]

Normal:

- LVEF > 55%

HF with reduced EF (HFrEF):

- HF with LVEF ≤ 40%

HF with mildly reduced EF (HFmrEF):

- HF with LVEF 41 to 49%

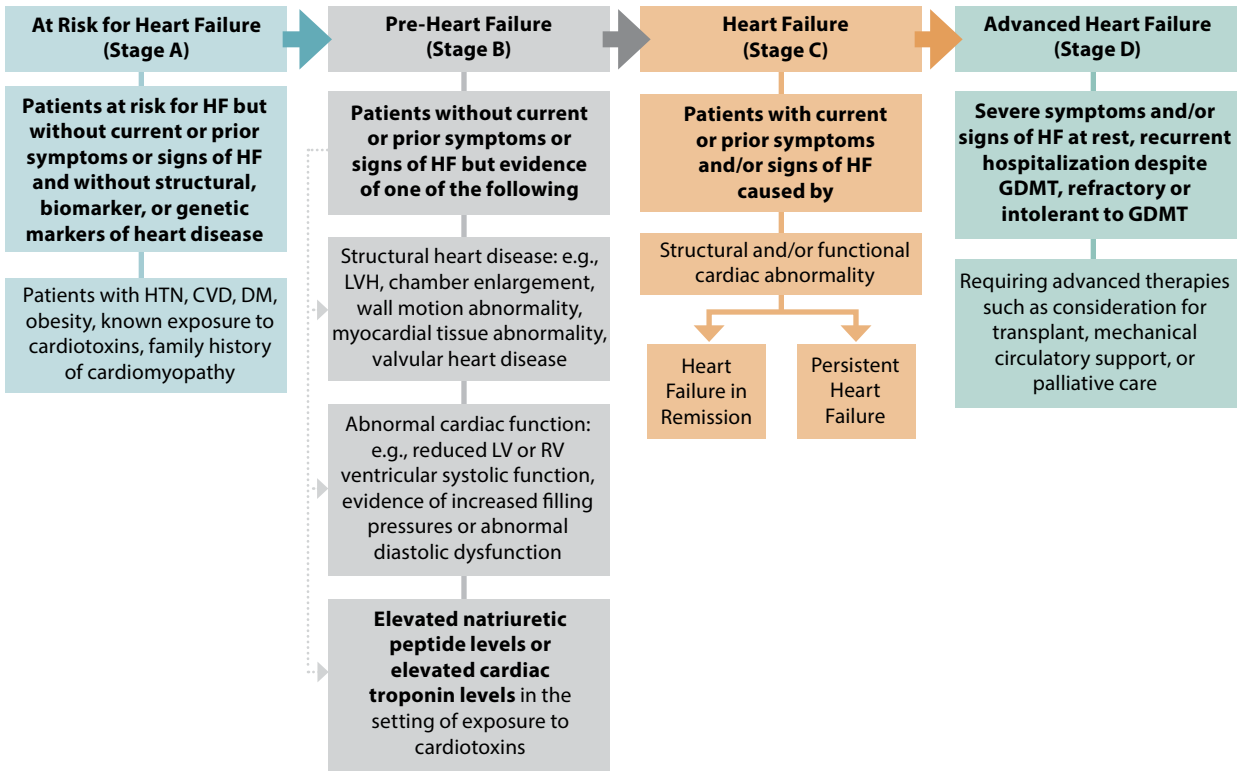
HF with preserved EF (HFpEF):

- HF with LVEF ≥ 50%

HF with improved EF (HFimpEF):

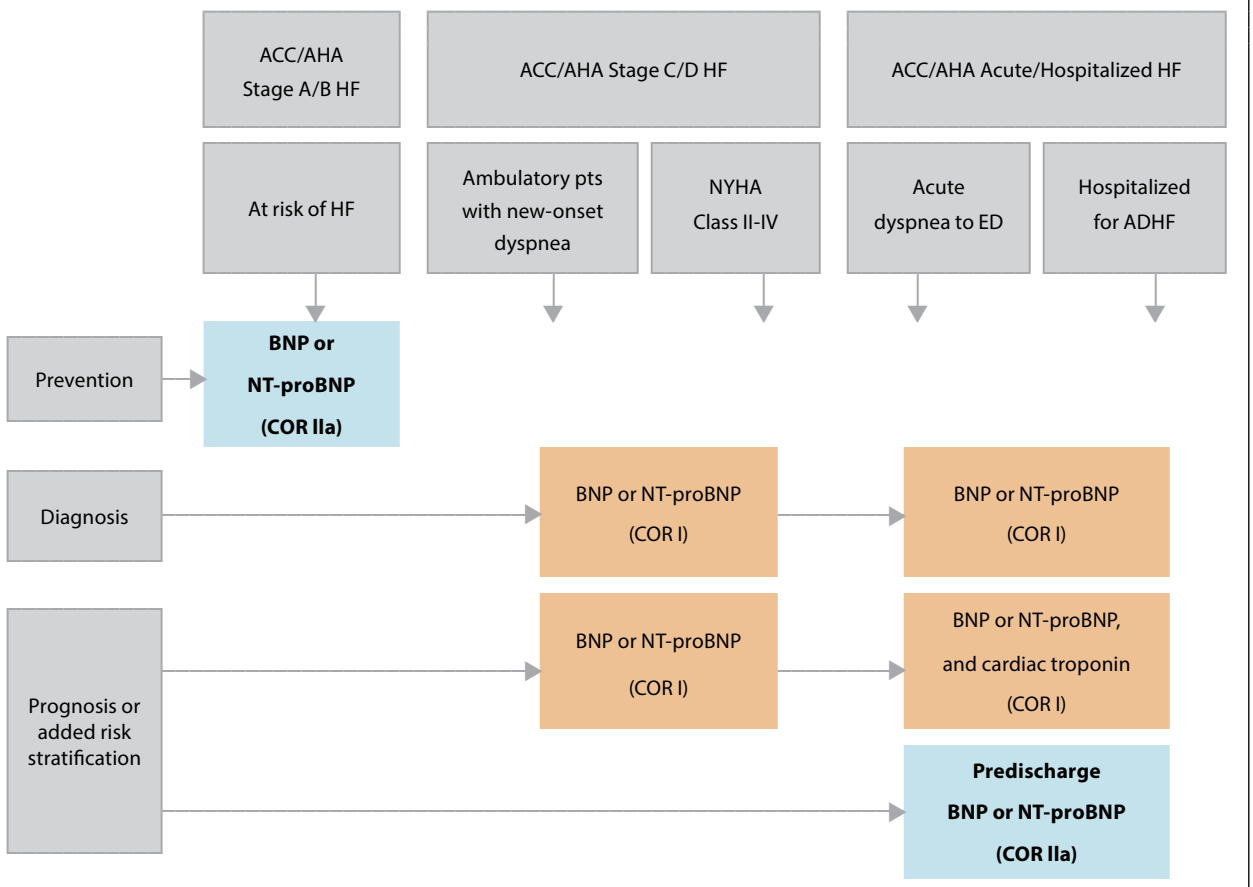
- HF with a baseline LVEF ≤ 40%, a ≥ 10 point increase from baseline LVEF and a second measurement of LVEF > 40%

Exhibit 2: New Classification of HF Stages[2]



HTN = hypertension; CVD = cardiovascular disease; DM = diabetes mellitus; HF = heart failure; LVH = left ventricular hypertrophy; LV = left ventricle; RV = right ventricle; GDMT = guideline-directed medical therapy

Exhibit 3: Biomarkers for Diagnosis and Prognosis in HF[3]



ACC/AHA = American College of Cardiology/American Heart Association; BNP = brain natriuretic peptide; NT = N-terminal; COR = class of recommendation; NYHA = New York Heart Association; ADHF = acute decompensated heart failure

College of Cardiology/American Heart Association recommended natriuretic biomarker testing for diagnosis and prognosis of HF.[3] Importantly, newer data suggest that natriuretic peptide biomarker screening and early intervention may prevent HF in those at risk (Stage A) or with pre-HF changes (Stage B).

Diagnosis of HF with preserved ejection fraction (HFpEF) may be more challenging to diagnose than HFrEF since testing parameters (e.g., BNP, electrocardiogram) are normal in some cases. There are two scoring systems (H2FPEF, HFA-PEFF) available to increase sensitivity to detect HFpEF based on clinical characteristics and diagnostic data. (H2FPEF is shown in Exhibit 4).[4]

The four pillars of guideline directed medical therapy (GDMT) for optimal management of HFrEF are an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker/neprilysin inhibitor combination (ARNI), a beta blocker, a mineralocorticoid receptor antagonist (MRA), and a sodium-glucose cotransporter 2 inhibitor (SGLT2i).[5,6] Sacubitril/valsartan is the only available ARNI and is only available as a brand name product. Each of these agents plays a role in modifying the pathophysiology of HF and have been shown to reduce morbidity and mortality. For selected patients with volume overload, a fifth agent, a diuretic, is added to reduce HF hospitalization and HF mortality. Other agents including isosorbide dinitrate or ivabradine may be added for specific indications. The guidelines and the Decision Pathway for Optimization provide specifics on how to initiate therapy, starting and target doses, and adherence management. Patients are not typically started on all four main agents at once but have them added over time.

Indications for use of an ARNI are HFrEF (EF < 40%), New York Heart Association (NYHA) class II–III HF, and administered in conjunction with a background of GDMT for HF for reduction of

Exhibit 4: H_2FPEF Scoring System[4]

	Clinical Variable	Values	Points
H_2	**Heavy**	BMI > 30 kg/m^2	2
	Hypertensive	Two or more antihypertensive medications	1
F	**Atrial Fibrillation**	Paroxysmal or Persistent	3
P	**Pulmonary Hypertension**	Doppler echocardiographic estimated pulmonary artery systolic pressure > 35 mmHg	1
E	**Elder**	Age > 60 years	1
F	**Filling Pressure**	Doppler Echocardiographic E/e' > 9	1
H_2FPEF score (≥ 6 or greater = ≥ 90% of HFpEF probability)			**Total (0 - 9)**

E/e' ratio is an index used to evaluate the left ventricle filling pressure

morbidity and mortality.[5] In patients with previous or current symptoms of chronic HFrEF, the use of ACE-I is beneficial to reduce morbidity and mortality when the use of ARNI is not feasible. In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACE-I because of cough or angioedema and when the use of ARNI is not feasible, the use of an angiotensin receptor blocker (ARB) is recommended to reduce morbidity and mortality. In patients with chronic symptomatic HFrEF NYHA class II or III who are currently tolerating an ACE-I or ARB, replacement by ARNI is recommended to further reduce morbidity and mortality.

The SGLT2i medication class was originally approved to treat type 2 diabetes but because of FDA required studies related to cardiovascular disease (CVD) risk and diabetes medications, these agents now have FDA-approved labeling for reducing CVD morbidity and mortality and HF hospitalizations. Several randomized control trials (RCTs) in patients with type 2 diabetes and either established CVD or high risk for CVD have shown that SGLT2i prevents HF hospitalizations compared with placebo.[7-9] An overall 31 percent reduction in HF hospitalizations was noted irrespective of the presence or absence of preexisting HF, although only 10 percent to 14 percent of participants had HF at baseline. The benefit appears independent of the glucose-lowering effects. In the DAPA-HF and EMPEROR-Reduced trials where the subjects had HFrEF, SGLT2i compared with placebo reduced the composite of cardiovascular death or HF hospitalization by approximately 25 percent.[10-11] The benefit in reduction of HF hospitalization was significant (30%) in both trials. Risk of cardiovascular death was significantly lowered (18%) with dapagliflozin, as was risk of all-cause mortality (17%). Although no significant cardiovascular mortality benefit was observed with empagliflozin in a meta-analysis of DAPA-HF and EMPEROR-Reduced trials, SGLT2i therapy was associated with a reduction in all-cause mortality and cardiovascular death.[12] The benefits in both trials were seen irrespective of baseline diabetes status. Furthermore, serious renal outcomes were less frequent, and the rate of decline in eGFR was slower in patients treated with SGLT2i. In patients with symptomatic chronic HFrEF, SGLT2i therapy is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes.[5] In patients with symptomatic chronic HFrEF, SGLT2i therapy provides intermediate economic value.[5]

ARNI and SGLT2i have also been evaluated across the spectrum of EF below normal. In selected patients with HFpEF, ARNI may be considered to decrease hospitalizations, particularly among patients with EF on the lower end of this spectrum.[5] In patients with HFpEF, SGLT2i can also be beneficial in decreasing cardiovascular mortality. EMPEROR-Preserved showed a significant benefit of the SGLT2i empagliflozin, in symptomatic patients with HF with EF > 40 percent and elevated

natriuretic peptides.[13] The 21 percent reduction in the primary composite endpoint of time to HF hospitalization or cardiovascular death was driven mostly by a significant 29 percent reduction in time to HF hospitalization (nonsignificant lower cardiovascular death [HR, 0.91; 95% CI, 0.76 to 1.0]), with no benefit on all-cause mortality. Empagliflozin also resulted in a significant reduction in total HF hospitalizations, decrease in the slope of the kidney function decline, and a modest improvement in quality of life at 52 weeks. Of note, the benefit was similar irrespective of the presence or absence of diabetes at baseline.

Multidisciplinary, comprehensive HF management programs can improve outcomes in HF. Patients with worsening or advanced HF should be referred to a comprehensive specialty program. A HF specialty team reviews HF management, assesses suitability for advanced HF therapies, and uses palliative care including palliative inotropes where consistent with the patient's goals of care. Clinical clues that a patient may have worsening or advanced HF include persistent NYHA III-IV symptoms; two or more emergency department visits or hospitalizations for acute HF in past 12 months; high-risk biomarker profile (hyponatremia, very or persistently elevated troponin or BNP/NT-proBNP), inability to uptitrate GDMT because of hypotension (SBP ≤ 90 mm Hg), dizziness, or worsening renal function; onset of arrhythmias (atrial fibrillation, ventricular tachycardia, ICD shocks); escalating doses of diuretics (e.g., > 160 mg/d furosemide) or persistent edema despite escalating diuretic doses and/or need for intravenous inotropes.[14]

Conclusion

The landscape of medical therapies available for treatment of HFrEF and HFpEF continues to rapidly evolve. Four-pillar guideline directed therapy (ARNI/beta-blocker/MRA/SGLT2i) is the standard of care for HFrEF. There are demonstrated benefits of ARNI and SGLT2i across the spectrum of EF below normal, which includes a subset of those with HFpEF so these agents will continue to be more frequently used. Morbidity, mortality, and hospitalizations can be reduced through a multidisciplinary, comprehensive disease management program.

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The Latest Evidence on Emerging Therapies and Innovations in Pulmonary Arterial Hypertension Management

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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

Pulmonary arterial hypertension (PAH) is a rare, incurable, and expensive to manage disease. Multiple PAH specific medications are available to reduce disease progression. In order to optimize management of this disease, referral to a PAH specialty center is important for appropriate diagnosis and medication selection.

Key Points

- PAH requires aggressive management.
- Combination therapy with two medications is standard first-line treatment.
- Initial treatment with triple therapy is appropriate for high-risk patients.
- Managed care should work with providers to optimize treatment and adherence.

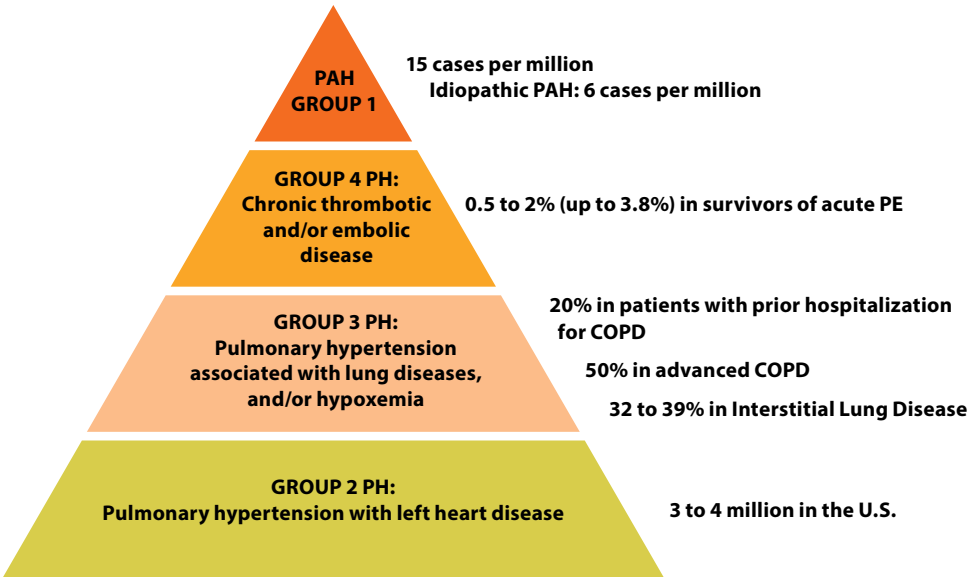
PULMONARY HYPERTENSION (PH) DESCRIBES a group of severe pulmonary vascular disorders characterized by elevated mean pulmonary arterial pressure (mPAP) at rest. The World Symposium on Pulmonary Hypertension categorizes pulmonary hypertension into five groups.[1] Pulmonary arterial hypertension (PAH), which corresponds to Group 1 PH, is the focus of this article.

PAH is a complex and devastating disease that causes progressive vasoconstriction and vascular remodeling of the distal pulmonary arteries.[2] Currently, there is no cure, and the majority of patients with PAH develop right heart dysfunction leading to death. PAH includes several subgroups, all having similar pulmonary vascular pathobiology, clinical characteristics, and management strategies. These include idiopathic, heritable, drug and toxin induced, PAH associated with HIV, connective tissue disease, portal hypertension, schistosomiasis, and congenital heart disease.

PAH is rare and as shown in Exhibit 1, there are approximately 15 cases per million people of which six cases per million are idiopathic PAH.[3] Overall, idiopathic, and heritable make up greater than 50 percent of cases.[2] PAH most often affects women aged between 30 and 60 years. It can occur in males and is often associated with worse clinical outcomes. From a National Institutes of Health registry in the 1980s, mean age of PAH presentation was 36 years, and the patients were primarily Caucasian.[4] Before specific treatments were available, median survival was 2.8 years after diagnosis. Data from the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) found that females accounted for 79.5 percent of cases, with the mean duration between symptom onset and diagnosis of 2.8 years, and a one-year survival rate of 91 percent after diagnosis.[5] Long-term survival (from data between March 2006 and December 2009) found survival rates of 85 percent at year three, 68 percent at year five, and 49 percent at year seven from time of diagnosis.[6]

The typical symptom of PAH is shortness of breath following exertion which could be caused by any

Exhibit 1: Pulmonary Hypertension Prevalence[3]



number of conditions; this non-specific symptom accounts for much of the delay in diagnosis. Other symptoms can be fatigue, weakness, chest pain, and dizziness. As the disease progresses, dyspnea at rest and symptoms of right heart failure occur.

Patients suspected of having PAH need to undergo extensive diagnostic testing. The patient's journey can be complex and prolonged. Diagnosis of PAH requires a right heart catheterization to demonstrate a mean pulmonary artery pressure (mPAP) greater than or equal to 20 mmHg at rest and a pulmonary vascular resistance (PVR) greater than or equal to 3 Wood units.[2]

Based on the incidence of PAH, a hypothetical health plan with five million patients can expect to have between 60 and 250 patients with PAH, and 12 to 38 new cases diagnosed annually. Early diagnosis is an important first step to ensure optimal treatment outcomes, however, misdiagnosis is common. Unfortunately, misdiagnosis leads to inappropriate treatment with expensive therapies that may negatively impact patients, avoidable economic expenses, and allows for unchecked disease progression. Treatment at a later stage of disease is associated with increased rates of hospitalization and length of stay plus added costs associated with treating PAH.[7]

The economic impact of PAH can be substantial. Estimated direct per-patient per-month costs for PAH are four to five times higher than matched control patients with similar age, gender, geographic region, and employment status.[8] A Kaiser Permanente Colorado review found the median total per-patient per-day and three-year total expenditures for patients with PAH to be $56 and $50,599, respectively.[9] A recent database study found only 21.0 percent of members received combination therapy as their first-line treatment as recommended by treatment guidelines, while most (54.6%) received combination therapy as second-line treatment.[10] This trial found that all-cause healthcare resource utilization remained high after treatment initiation with 58.0 percent of members having one or more hospitalizations and 41.3 percent with one or more emergency room visits which suggests poor disease control.[10] Total all-cause costs declined from $15,117 per patient per month at baseline to $14,201 after treatment initiation, with decreased medical costs ($14,208 versus $6,349) more than offsetting increased pharmacy costs ($909 versus $7,852). Another trial showed the same pattern of declining total costs with treatment despite increased pharmacy costs.[11] Rehospitalization contributes to overall costs in PAH. In one trial, 79.3 percent of those studied had at least one rehospitalization within one year of an index hospitalization.[12] Over 20 percent of those with rehospitalization had three or more admissions.

Management of PAH is multifaceted and consists of supportive therapy as well as advanced vasodilatory therapy.[13] Multiple PAH-specific vasodilatory therapies have been developed, and all currently target one of three pathways that contribute to endothelial dysfunction – prostacyclin, endothelin,

Exhibit 2: Assessing Risk in PAH[14]

Determinants of prognosis[a] (estimated1-year mortality)	Low Risk < 5%	Intermediate Risk 5% to 10%	High Risk > 10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	> 440 m	165 - 440 m	< 165 m
Cardiopulmonary exercise testing	Peak VO_2 > 15 mL/min/kg (> 65% pred.) VE/VCO_2 slope < 36	Peak VO_2 > 11 - 15 mL/min/kg (35% - 65% pred.) VE/VCO_2 slope 36 - 44.9	Peak VO_2 < 11 mL/min/kg (< 35% pred.) VE/VCO_2 slope ≥ 45
NT-proBNP plasma levels	BNP < 50 ng/L NT-proBNP < 300 ng/L	BNP 50 - 300 ng/L NT-proBNP 300 - 1,400 ng/L	BNP > 300 ng/L NT-proBNP > 1,400 ng/L
Imaging (echocardiography, CMR imaging)	RA area < 18 cm^2 No pericardial effusion	RA area 18 - 26 cm^2 No or minimal pericardial effusion	RA area > 26 cm^2 Pericardial effusion
Hemodynamics	RAP < 8 mm Hg CI ≥ 2.5 L/min/m^2 SvO_2 > 65%	RAP 8 - 14 mm Hg CI 2.0 - 2.4 L/min/m^2 SvO_2 > 60% - 65%	RAP > 14 mm Hg CI < 2.0 L/min/m^2 SvO_2 < 60%

6MWD = 6-minute walking distance; BNP = brain natriuretic peptide; CI = cardiac index; CMR = cardiac magnetic resonance; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; pred. = predicted; RA = right atrium; RAP = right arterial pressure; SvO_2 = mixed venous oxygen saturation; VE/VCO_2 = ventilatory equivalents for carbon dioxide; VO_2 = oxygen consumption; WHO = World Health Organization.

[a]Most of the proposed variables and cutoff values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for idiopathic PAH and the cutoff levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.

[b]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.

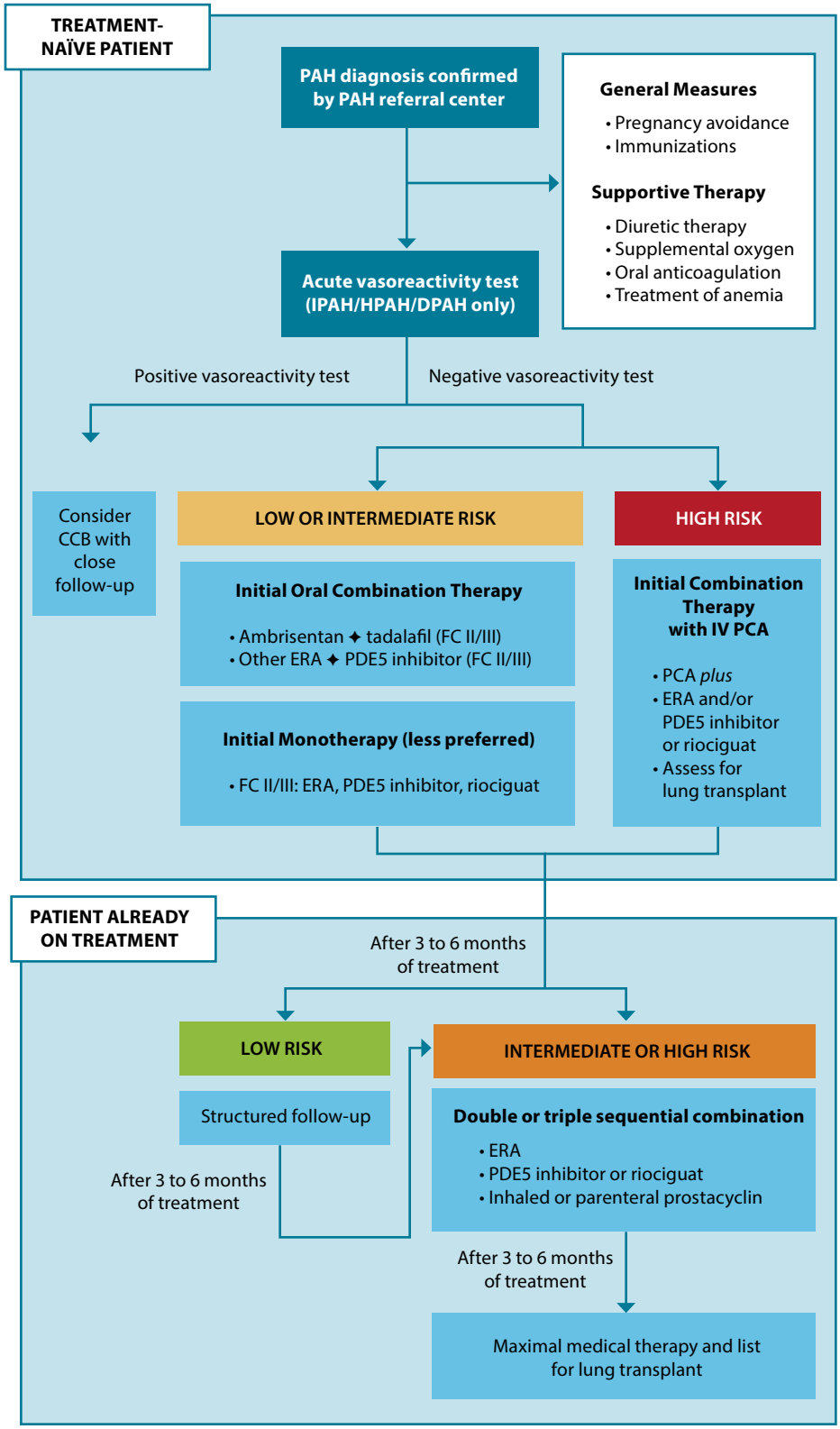
[c]Repeated episodes of syncope, even with little or regular physical activity.

and nitric oxide pathways. The prostacyclin agents include inhaled iloprost; inhaled, oral, and parenteral treprostinil; parenteral epoprostenol; and oral selexipag. The endothelin receptor antagonists (ERA) are ambrisentan, bosentan, and macitentan, all of which are oral agents. Sildenafil and tadalafil are oral phosphodiesterase-5 (PDE5) inhibitors and riociguat is a soluble guanylate cyclase stimulator. Effective therapy should be instituted in the initial stages of the disease, before irreversible changes in pulmonary vasculature occur. Supportive therapy may include oxygen therapy, diuretics, exercise, anticoagulation, and treatment of anemia. To decrease the risk of developing pneumonia, the cause of death in 7 percent of patients with PAH, patients should receive vaccinations against influenza, COVID-19 and pneumococcal pneumonia.

Before PAH specific medications are started, vasoreactivity testing should occur in those with idiopathic, heritable, and drug- or toxin-induced PAH. Testing is done to determine whether high-dose calcium channel blockers (CCBs) are a treatment option. Ten to 20 percent of patients will have a positive or vasoreactive response and are considered eligible for CCBs. Commonly used CCBs include nifedipine 30 mg daily or diltiazem 120 mg daily increased to the maximum tolerated dose over days to weeks. The benefits of CCBs typically only lasts about one year.

Individuals who are considered non-vasoreactive will be initiated on pharmacotherapy with single or dual combination therapy according to risk status, functional class, and patient preference.[13] Risk assessment determines if a person with PAH has a low, intermediate, or high risk of one-year mortality (Exhibit 2).[14] The 2019 CHEST guidelines contain a treatment algorithm that guides clinical decision making based on patient functional class, disease

Exhibit 3: Treatment Algorithm[13]



CCB= calcium channel blocker; DPAH =drug-induced pulmonary arterial hypertension; ERA = endothelin receptor antagonist; FC = functional class; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary hypertension; PAH = pulmonary hypertension; PCA = prostacyclin analog; PDE = phosphodiesterase

progression, and response to treatment (Exhibit 3).[13] In treatment-naïve patients with low or intermediate risk of death within one year, the preferred treatment is dual combination with an ERA and a PDE5 inhibitor. Combination of these two classes has been shown to decrease disease progression and hospitalization. Only trials of the parenteral prostacyclins have demonstrated survival gains. Patients with high-risk disease are typically started on triple therapy with parenteral prostanoid, ERA, and PDE5 inhibitor or riociguat but dual therapy is an option. For patients who progress or respond poorly to initial therapy, practitioners typically add agents from a different class. Agents within the same class (including PDE5 inhibitors and guanylate cyclase stimulators) should not be used together.

Disease-modifying agents that can alter the course of the disease are certainly needed to improve outcomes and continuous progress in the understanding of the pathophysiology of PAH offers exciting opportunities for the development of new therapeutic targets. The future goal is to continue to improve long-term survival. Ralinepag, one of the investigational agents, is a next-generation, orally available, non-prostanoid, selective and potent prostacyclin receptor agonist. Sotatercept is a fusion protein that binds to and sequesters select transforming growth factor β superfamily ligands proposed to rebalance anti-proliferative and pro-proliferative signaling. In preclinical models of PAH, sotatercept has been shown to reverse pulmonary arterial wall and right ventricular remodeling. Other agents under development include imatinib which targets platelet-derived growth factor signaling, pemziviptadil which is a subcutaneously-injected vasoactive intestinal peptide analogue, and bardoxolone which acts as an activator of the NF-E2-related factor 2 (Nrf2) pathway and an inhibitor of the nuclear factor kappa-light-chain-enhancer of activated B (NF-κB) pathway.

In managing patients with PAH, payers must consider a patient-centered approach that takes into account the impact of this illness on day-to-day activities and quality of life.[15] Managed care should encourage early referral to expert centers to accurately diagnose and initiate treatment and work collaboratively with multiple healthcare providers, including primary care, in order to help optimize patient outcomes. Educational initiatives on PAH may be helpful, but it may be hard to get a primary care provider's attention on an uncommon and hard to diagnose illness. Referrals to PAH care centers are often delayed and continue to be problematic. Patients are often referred with incomplete diagnostic testing, misdiagnosis, and inappropriate treatment and are not referred until their disease has progressed significantly.[16] They may be inappropriately diagnosed with asthma or chronic obstructive pulmonary disease.

The evolution in the PAH treatment guidelines demands early and aggressive treatment backed by robust clinical trials. Restrictive payer management strategies may have unintended negative outcomes on patients with PAH because of small patient numbers and limited clinical understanding of evolving evidence on treatment options.[17]

Managed care professionals in the specialty care setting can also play an important role in impacting medication adherence. These therapies are very costly, so it is even more crucial to ensure that patients are taking the medications appropriately. Additionally, closely following these patients may play an important role in preventing rehospitalizations, for which patients with PAH are at high risk. One retrospective study of adult patients with PAH who were prescribed PDE5 inhibitor therapy and who received medication management through the center's specialty pharmacy found that 94 percent of the patients achieved optimal medication adherence.[18]

Conclusion

PAH is a fatal disease that requires aggressive management. Treatment guidelines recommend combination therapy from the beginning for most patients, regular assessment, and escalating care in patients not at goal of low-risk status. Adherence monitoring and intervention is important in providing optimal outcomes from therapy.

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Patient-Focused Treatment Decisions in the Management of HIV: Individualizing ART Decision Making for Improved Clinical and Economic Outcomes

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

Summary

There are several new therapies for HIV infection which are improving the patient burden and providing treatment options for those who are heavily treatment experienced. Integrating these options into managed care plans is important.

Key Points

- Several options are recommended for initial treatment of newly diagnosed people.
- Most clinicians and patients choose a once a day, triple agent combination.
- Three agents are also available for those with multidrug resistance.
- Long-acting injectable antiretroviral medications are now available but can be logistically difficult for providers to implement.

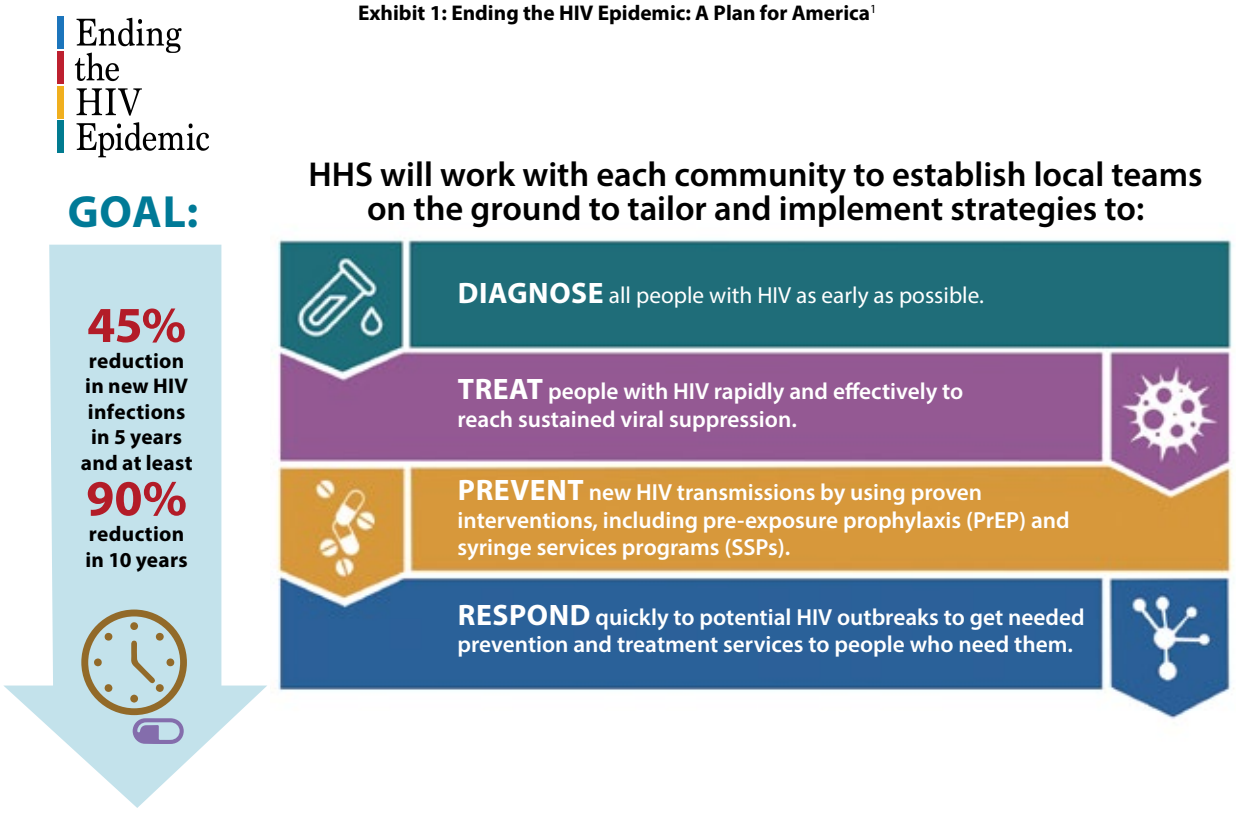
FROM A PUBLIC HEALTH STANDPOINT, there is a multipronged approach recommended to end the HIV epidemic in the United States (U.S.). The components are expanded testing for early diagnosis of all who are infected, treating for rapid and sustained viral suppression, preventing HIV infection in at-risk individuals, and targeting resources to respond to outbreaks (Exhibit 1).[1]

The number of new HIV infections in the U.S. has been relatively steady at 38,000 each year for the last 15 years.[1] In 2016–17, greater than 50 percent of new HIV diagnoses occurred in 48 counties across the country plus Washington, DC, and San Juan, Puerto Rico. Seven states have a high rural burden accounting for greater than 75 percent of cases and greater than or equal to 10 percent of diagnoses in rural areas. These are the areas that are being targeted by federal prevention programs.

Gaps persist across the HIV care continuum in the U.S. About 86 percent of estimated cases in the U.S. get diagnosed.[2] Of those who get diagnosed, 64 percent receive care and only 53 percent achieve viral suppression. To increase diagnosis, testing should be offered to everyone who interacts with a component of the healthcare system. The entity who does the testing should then ensure any positive individuals get into HIV care. Many localities in the U.S. try to start medication the day of diagnosis. Moving from diagnosis to sustained HIV care with continued viral suppression is a challenge in the U.S. Once virally suppressed, people do not transmit HIV. There are significant barriers to accessing care especially among people of color (Exhibit 2).

Rapid initiation of antiretroviral therapy (ART) at the time of diagnosis has been shown to provide significant benefits. Compared with standard care, same-day ART increases likelihood of ART continuation, patient retention in care, and viral suppression at 12 months.[3] It also reduces the risk of death from HIV within 12 months of diagnosis

Exhibit 1: Ending the HIV Epidemic: A Plan for America[1]



and faster viral suppression.[3,4] Although it is not always feasible to do same day ART starts, the goal should be to get those diagnosed on medication as soon as possible.

Initial ART options in a treatment naïve person are shown in Exhibit 3.[5] A combination of antiretrovirals (ARVs) with different mechanisms of action are required to prevent HIV resistance from developing. Bictegravir/tenofovir alafenamide/emtricitabine is the most commonly used option and is a single tablet taken once daily. Once-daily regimens have led to an enormous reduction in patient burden compared to some of the older ART regimens. The second and fourth options in Exhibit 3 are also once-daily regimens but prescribing these requires genetic resistance, and/or hepatitis B testing before starting therapy. Patients are often interested in the two drug regimen since it contains fewer medications; there are no data to say that the two drug regimen is any safer long-term than the three drug regimens. It is important to note that although tenofovir disoproxil fumarate (TDF) is included as an option in the guidelines, most clinicians preferentially use tenofovir alafenamide (TAF), because of bone loss and kidney dysfunction with TDF, for chronic treatment.

Long-acting injectable ARVs are now available. The two medication regimen of long-acting injectable cabotegravir and long-acting injectable rilpivirine is indicated as a complete regimen for the treatment of HIV infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV RNA less than 50 copies per mL) on a stable ART regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. This regimen is equivalent to once daily oral ART regimens.[6,7]

Resistance can occur with this long-acting regimen compared to bictegravir- or dolutegravir-based daily regimens which do not produce resistance.[8] Cases of resistance have been seen in countries other than the U.S. This agent can be started with an oral lead-in before injectable is started or directly with injection. Injectable therapy is given as monthly or every two-month intramuscular injections (each medication requires a separate intramuscular injection). Patients with baseline rilpivirine resistance associated mutations, A1 or A6 HIV subtype—which is not typically seen in U.S.— or body mass index (BMI) > 30 are more likely to have failure with every two-month regimens. The issue with high BMI can be overcome by using a longer needle to actually

Exhibit 2: Assessing Barriers to Care and Treatment

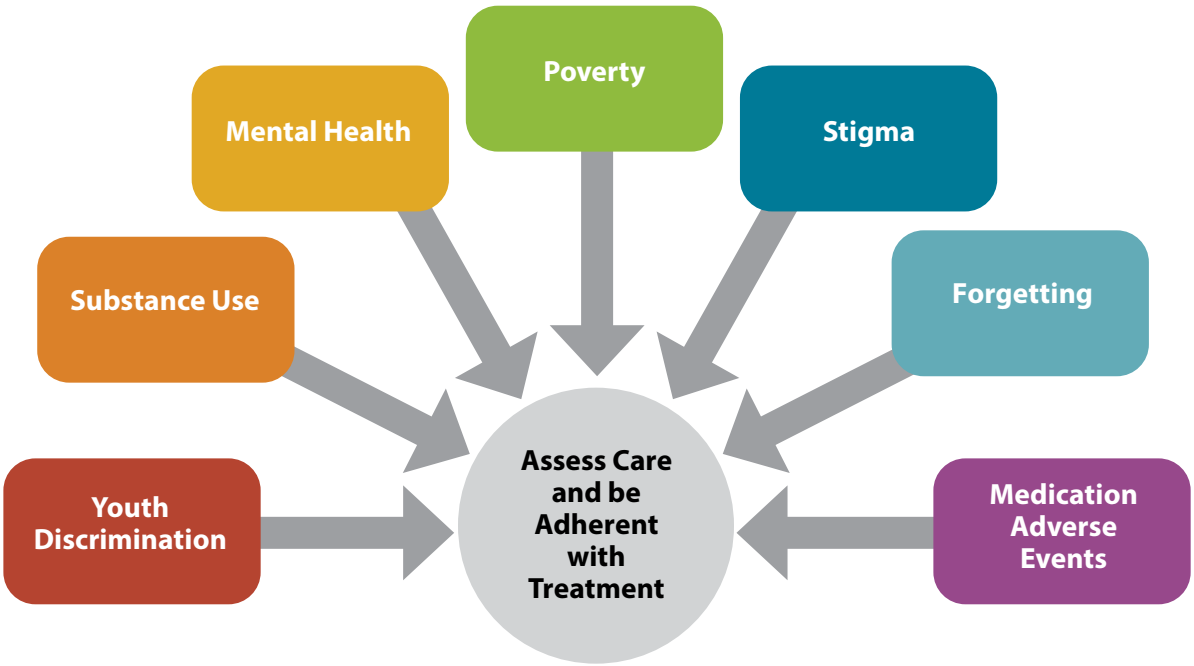


Exhibit 3: DHHS Regimen Recommendations for Initial ART[5]

Regimen	Pros	Cons
Bictegravir/tenofovir alafenamide/emtricitabine	Excellent activity over 5 years, no resistance, 1 pill daily, tolerable, can use with CrCl down to 30 mL/min.	Weight gain
Dolutegravir/abacavir/lamivudine	Comparable virologic activity, no resistance, 1 pill daily, CrCl down to 30 mL/min	Genetic testing required, increased CV risk, weight gain, not appropriate for HBV.
Dolutegravir plus (emtricitabine or lamivudine) plus (tenofovir alafenamide [TAF] or tenofovir disoproxil fumarate [TDF])	Excellent activity over 5 years, no resistance, tolerable, CrCl down to 30 mL/min, a preferred regimen for pregnancy [TAF], 2 pills daily	Weight gain
Dolutegravir/lamivudine	Excellent activity over 3 years, no resistance, tolerable, CrCl down to 30 mL/min, 1 pill daily	Weight gain Not for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or when ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

HBV = hepatitis B virus; ART = antiretroviral therapy; CV = cardiovascular; CrCl = creatinine clearance

deposit medication into the muscle instead of adipose tissue. This combination may be an option for those who prefer not to take daily medications or have adherence issues. Trials have examined use of this combination in treatment naïve patients as initial therapy but this is not yet an FDA-approved indication.

There is a small population of people with HIV who are heavily treatment experienced (HTE) and have multidrug resistance (MDR). These patients generally started therapy in the 1990s with subpar regimens, have been treated with many different agents, and have accumulated resistance. They have resistance to two or more medications and three or more classes. It can be difficult to construct an effective regimen for these people. Resistance testing is done to identify an effective regimen. A new regimen can include two fully active drugs if at least one with a high resistance barrier is included (e.g., dolutegravir or boosted darunavir).[5] If no fully active drug with a high resistance barrier is available, then every effort should be made to include three fully active drugs.

Three newer therapies are specific for HTE adults with MDR. Fostemsavir is a novel oral ARV indicated for combination therapy in HTE adults with known MDR HIV, specifically for patients who are failing current ART due to potential resistance, intolerance, or safety considerations. It is the first FDA-approved attachment inhibitor. After enzymatic activation to the active molecule temsavir, it binds to gp120 which prevents viral entry into CD4 cells, effectively stopping viral replication.

Ibalizumab is an injectable recombinant monoclonal antibody that binds to the surface proteins of CD4 cells leading to conformational changes that prevent the steps required for HIV fusion and entry into the cell. Because of its unique binding specificity, ibalizumab blocks viral entry without causing immunosuppression. It is indicated in combination with other ARVs for treatment in HTE adults with MDR HIV who are failing their current ART regimen.

Lenacapavir is the first HIV capsid inhibitor and is the most recent FDA approval (12/2022) for HTE adults with MDR HIV. Interestingly, this agent is started with both oral and subcutaneous loading doses and then subcutaneous doses are given every six months. Future treatment options are long-acting lenacapavir with another injectable long-acting to form a complete regimen as a long-acting option for those who are not HTE or with MDR .

Conclusion

Several ART options are recommended by the national treatment guidelines for initial treatment of newly diagnosed people. Most clinicians and patients choose a once a day, triple agent combination. Three agents are also available to add to ART for those with multidrug resistance. Long-acting injectable ARTs are now available and an option for some patients. Clinicians have to figure out how to logistically implement the injectable agents which are given infrequently.

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Confronting the Clinical and Economic Burden of Atopic Dermatitis: Managed Care Considerations on the Evolving Role of JAK Inhibitors

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Summary

The treatment of atopic dermatitis (AD) has undergone significant changes since 2017. There are now two injectable biologics and two oral Janus Kinase (JAK) inhibitors for moderate-to-severe disease and a topical JAK inhibitor for mild-to-moderate disease. More agents are on the way which will further complicate management of AD.

Key Points

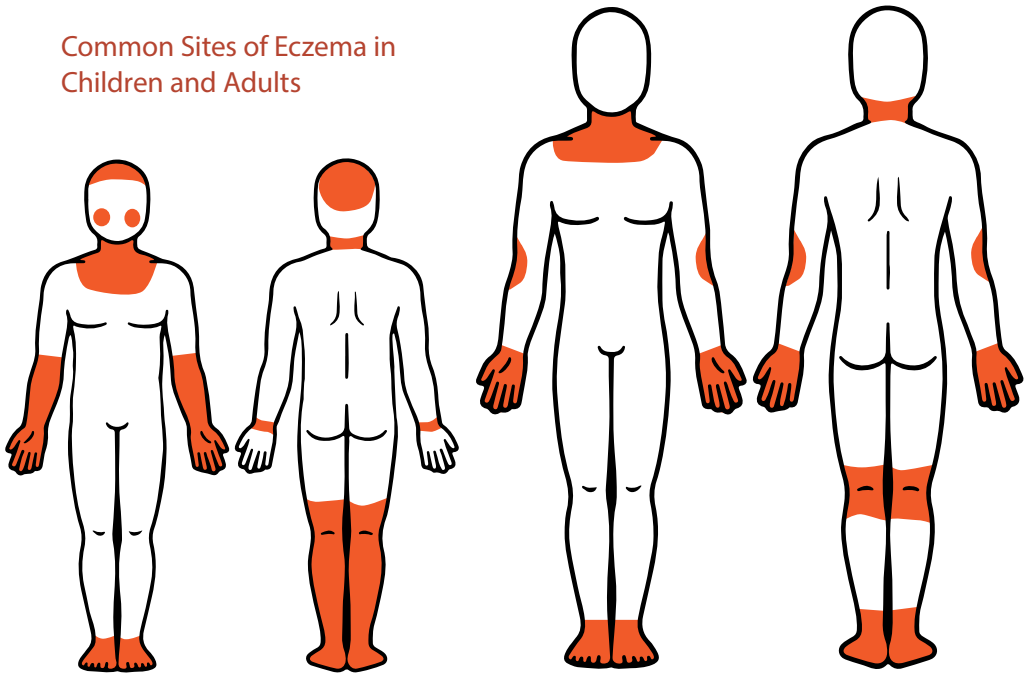
- Dupilumab and tralokinumab are the available injectable biologics.
- Upadacitinib and abrocitinib are the available oral JAK inhibitors.
- There are limited comparative data on the four agents for moderate-to-severe AD.
- Ruxolitinib is a topical JAK inhibitor effective for mild-to-moderate AD.

ATOPIC DERMATITIS (AD) IS A CHRONIC, pruritic inflammatory skin condition which typically affects the face, neck, arms, and legs but usually spares the groin and axillary regions (Exhibit 1).[1] It usually starts in early infancy, but also affects a substantial number of adults. AD is commonly associated with elevated levels of immunoglobulin E (IgE) and other allergic (atopic) diseases such as asthma.[2] The major symptom is pruritus and a relapsing disease course is common.

Generally, the diagnosis is made by clinical assessment. Importantly, AD is often indistinguishable from other causes of dermatitis. In infancy, the most common difficulty is distinguishing it from seborrheic dermatitis. Both AD and seborrheic dermatitis have to be distinguished from psoriasis. No reliable biomarker exists for the diagnosis of AD and laboratory testing is seldom necessary but a complete blood cell count can be useful to exclude immune deficiency.[3] An IgE level can be helpful to confirm an atopic pattern. Skin swab cultures can be helpful to identify *Staph aureus* superinfection. Allergy and radioallergosorbent testing are of little value. Biopsy shows an acute, subacute, or chronic spongiotic dermatitis pattern that is nonspecific but can be helpful to rule out other conditions (e.g., cutaneous T-cell lymphoma).

In the United States (U.S.) an estimated 31.6 million people have AD with 17.8 million of those having moderate-to-severe disease.[4] It affects 15 to 30 percent of children with 60 percent of those affected developing the disease within one year of birth.[5] Approximately one out of every three children with AD have moderate-to-severe disease. About 70 percent of children will have spontaneous remission by adolescence but AD can come back in adulthood. Importantly, 50 percent of children with AD will develop asthma.[6] This is not solely a disease of childhood onset as one in four adults with AD report adult-onset of initial symptoms. Eleven percent of U.S. adults have moderate-to-severe AD requiring systemic therapy.[7] The prevalence of AD is much higher than for psoriasis. AD affects a similar number of male and female children, however, studies have shown it is more common in adult females than males.[4]

Exhibit 1: AD Clinical Presentation



In the U.S., AD affects more African-American children and European-American children compared to Hispanic children.[4] African-American and Hispanic children tend to have more severe AD compared to European-American children. Children born outside the U.S. have a 50% lower risk of developing AD, that is increased after living in the U.S. for 10 years. Although study percentages vary, adults that are multiracial or white tend to have the highest prevalence.

AD has a significant quality of life impact on those affected and in the case of children, their parents. Greater than 30 percent of patients report sleep disturbances because of pruritis and over 75 percent report that the disease affects activities of daily living.[6] More than 50 percent are frustrated by lack of disease control.

Little data on the economic costs of treating AD were available prior to biologics being approved by the FDA in 2017. Third-party payer cost in 1998 was estimated to be $0.9 billion to $3.8 billion annually for those under 65 years of age.[8] A study using 2018 data found that adults with AD had greater utilization of outpatient services, outpatient pharmacy services, and short-term disability benefits than those without AD. Unadjusted annual healthcare costs in 2018 were $4,979 higher for adults with AD ($14,603) than for the matched controls ($9,624), primarily driven by outpatient services and pharmacy costs.[9] Another study found that mean annualized total costs for those with moderate-to-severe AD were $20,722 of which $11,196 were medical costs ($7,973 in outpatient visit costs) and $9,526 were pharmacy costs.[10] Those treated with a biologic (dupilumab) had the highest mean annualized total cost at $36,505. The addition of biologics to the treatment options has substantially increased costs.

The epidermis of AD patients is characterized by significant barrier disruption. An intact, healthy skin barrier is a critical first-line of defense against various microbes, irritants, and allergens. AD patients have an increased susceptibility to allergic sensitization as well as microbial colonization and infections. AD is thought to be the result of immune dysregulation and impaired skin barrier function.[11,12] Multiple inflammatory cells and cytokines are involved in the disease process. Barrier disruption of the epidermis leads to T cell-related inflammation and ultimately chronic changes, leading to more inflammation. T-helper cell two (Th2) factors that play a role in AD include interleukin 4 (IL-4), IL-13, and IL-31 (which is known as the itch interleukin). IL-4 and IL-13 are elevated in acute and chronic skin lesions of AD and high levels of IL-4 and IL-13 act as inhibitors of filaggrin gene expression and antimicrobial peptides in the skin.[13] The Janus

kinase (JAK)-signal transducer and activator of transcription (STAT) pathway has been shown to play an essential role in the dysregulation of immune responses in AD including exaggeration of Th2 cell response, activation of eosinophils, maturation of B cells, and suppression of regulatory T cells.[14] This pathway, activated by IL-4, upregulates epidermal chemokines, pro-inflammatory cytokines, and pro-angiogenic factors and downregulates other factors responsible for skin barrier function. Current FDA-approved agents target IL-4, IL-13, and JAK-STAT. Agents targeting other pathways are also under investigation.

Before the biologic era there were limited treatments for AD, especially moderate-to-severe disease. Moisturization and maintenance of intact skin barrier, topical corticosteroids, and topical calcineurin inhibitors were the main therapies. Non disease specific systemic therapy options including methotrexate, azathioprine, and cyclosporine were the only options once a patient failed less conservative therapies. Despite those therapeutic options, treatment of AD often was sub-optimal.

Moisturization and maintenance of the intact skin barrier remain a cornerstone of treatment. Topical corticosteroids are generally first-line treatment and topical calcineurin inhibitors may be used with or without topical corticosteroids. Once first-line therapy has failed, patients then move on to biologics or JAK inhibitors.

The first FDA-approved biologic for AD was dupilumab, a fully human monoclonal antibody that targets the IL-4 receptor alpha subunit that blocks the signaling of IL-4 and IL-13, both key cytokines in Th2-mediated pathways. It was first approved for adults with AD in 2017 and subsequently approved for adolescents in 2019 and children down to age six in 2020. In two Phase III trials, this agent significantly improved measures of skin clearing [Eczema Area and Severity Index (EASI) and Investigator Global Assessment (IGA)] and severity of disease at 16 weeks compared to placebo. There was a clearing or near clearing of skin lesions among 37.9 percent and 36.0 percent who received dupilumab compared with 8.5 and 10.3 percent in the placebo groups.[15] The dupilumab treatment groups had an average 35 percent more patients achieve EASI-75 (75 percent improvement in rash area and eczema severity) compared with placebo.[15] In addition to significantly improving the signs and symptoms of AD, including pruritus, those treated with dupilumab had improvement in symptoms of anxiety and depression and quality of life, as compared with placebo.

Tralokinumab, an anti-IL-3 agent, is the other injectable biologic for moderate-to-severe AD. In patients with moderate-to-severe AD, treatment with tralokinumab 300 mg every two weeks resulted in 26.7 percent achieving clear or near clear skin by IGA from baseline compared to 11.8 percent with placebo.[16] This 14.9 percent difference from placebo is less than what was seen in the dupilumab trials. The change in EASI score (compared to placebo) was -4.94 ($p = 0.01$). Greater responses were found in participants with higher concentrations of biomarkers of increased IL-13 activity. Use with topical corticosteroids improves efficacy of this agent.[17]

Ruxolitinib was the first JAK inhibitor approved by the FDA for AD and is a topical cream for the short-term treatment of mild-to-moderate AD in immunocompetent patients older than 12 years whose disease is not controlled with other topical prescription therapies. More patients with mild-to-moderate AD treated in groups with ruxolitinib achieved EASI-75 compared to placebo vehicle (62.1% versus 24.6%).[18] Clinically relevant reduction in pruritus was achieved. Adverse events occurred in approximately 30 percent of patients with burning and pruritus at the application site being the most common event.

Upadacitinib and abrocitinib are both oral JAK inhibitors which are FDA-approved for those 12 and older with refractory, moderate-to-severe AD whose disease is not adequately controlled with other systemic agents, including biologics, or when use of those therapies are inadvisable. For upadacitinib, EASI-75 was achieved in 65 percent of those on 15 mg daily, 61.5 percent on 30 mg, and 46.5 percent on placebo.[19] For abrocitinib, EASI-75 was achieved in 40 percent receiving 100 mg daily, 63 percent on 200 mg, and 12 percent on placebo.[20] One possible advantage of upadacitinib over abrocitinib in terms of managed care management is its wide range of indications (AD, rheumatoid arthritis, ulcerative colitis, radiographic and non-radiographic ankylosing spondylitis), whereas abrocitinib is currently only indicated for AD. Data from a large, randomized safety trial of patients with rheumatoid arthritis indicate that oral JAK inhibitors may increase the risk of serious infections, major cardiovascular events (heart attack, stroke), lymphoma, lung cancer, and thrombosis.[21] The potential risk of these adverse events must be considered before these agents are prescribed.

Abrocitinib and upadacitinib have been directly compared to dupilumab. As shown in Exhibit 2, abrocitinib at 200 mg daily produces higher rates on IGA and EASI-75 compared to dupilumab and placebo but no statistics were presented in the

Exhibit 2: Abrocitinib versus Dupilumab and Placebo[22]

838 Adults with atopic dermatitis unresponsive to topical agents	**IGA Response** (improvement of 2.2 points at 12 weeks)	**EASI-75 Response** (≥ improvement of at 12 weeks)
Abrocitinib, 200 mg/day (orally; n = 226)	**48.4%** $p < 0.001$ versus placebo	**70.3%** $p < 0.001$ versus placebo
Abrocitinib, 100 mg/day (orally; n = 238)	**36.6%** $p < 0.001$ versus placebo	**58.7%** $p < 0.001$ versus placebo
Dupilumab, 300 mg every 2 weeks (subcutaneously; n = 243)	**36.5%**	**58.1%**
Placebo (n = 131)	**14.0%**	**27.1%**

IGA = Investigator's Global Assessment; EASI-75 = Eczema Area and Severity Index-75

Exhibit 3: Incremental Cost-Effectiveness Ratios[24]

Intervention	Comparator	Cost per QALY Gained
Abrocitinib*	Standard of care	$148,300
Baricitinib	Standard of care	$71,600
Tralokinumab*	Standard of care	$129,400
Upadacitinib	Standard of care	$248,400
Dupilumab	Standard of care	$110,300
Abrocitinib*	Dupilumab	$303,400
Baricitinib	Dupilumab	Less Costly, Less Effective
Tralokinumab*	Dupilumab	Less Costly, Less Effective
Upadacitinib	Dupilumab	$1,912,200

*Placeholder price used since price was not yet set at time of review
QALY= quality adjusted life year

study comparing abrocitinib to dupilumab.[22] In a trial comparing upadacitinib and dupilumab, 71.0 percent and 61.1 percent of patients achieved EASI-75, respectively ($p = .006$).[23] Secondary endpoints also demonstrated superiority of upadacitinib versus dupilumab, improvement in pruritus as early as week 1 (31.4% versus 8.8%; $p < .001$), achievement of EASI-75 as early as week 2 (43.7% versus 17.4%; $p < .001$), and achievement of EASI-100 at week 16 (27.9% versus 7.6%; $p < .001$). Rates of serious infection, eczema herpeticum, herpes zoster, and laboratory-related adverse events were higher for patients who received upadacitinib, whereas rates of conjunctivitis and injection-site reactions were higher for patients who received dupilumab.

The Institute for Clinical and Economic Review (ICER) produced a report on effectiveness and value of biologics and JAK inhibitors in treating AD in August 2021. This review was before FDA approval of tralokinumab, abrocitinib, and upadacitinib. It also includes baricitinib which is currently FDA-approved for other indications but also under study

for AD. The review noted that in the moderate-to-severe population, the JAK inhibitors and biologics all improve skin findings compared with placebo, and where assessed, appeared to improve itch, sleep, and quality of life.[24] Quantitative indirect comparisons, as well as the head-to-head comparisons previously discussed, suggest that higher doses of upadacitinib and possibly abrocitinib are somewhat more effective than dupilumab, while baricitinib (at the doses likely to be approved) and tralokinumab are possibly somewhat less effective than dupilumab.[24] The review also notes that there is substantial uncertainty in these comparisons. Resolution of itch may occur more quickly with higher-dose abrocitinib than with dupilumab. The cost and effectiveness of abrocitinib, baricitinib, tralokinumab and upadacitinib for moderate-to-severe AD was compared to topical emollients (standard of care) and dupilumab, over a five-year time horizon taking a health system perspective (Exhibit 3).[24] All have substantial incremental cost-effectiveness ratios.

The entry of multiple biologics and JAK inhibitors in the AD treatment space creates a situation analogous to the introduction of biologics for other conditions such as rheumatoid arthritis and psoriasis. Payers will need to evolve their management strategy to allow access to the most appropriate treatment based on safety, efficacy and relative cost. Prior authorization programs will need to be developed based on labeled indications, prior therapies, and severity of disease. Payers must balance mode of administration (injectable versus oral), safety (box warnings for JAK inhibitors) and relative cost/outcomes with minimal comparative data. While some comparisons exist, the data remains incomplete for a total assessment of the biologic agents, especially with two injectables and two orals already in the space.

The cost of caring for patients with AD is growing, mainly due to the cost of biologic treatments for moderate-to-severe disease. A robust pipeline will further complicate this space. More data, especially real-world data, are needed to help improve management strategies of multiple AD drugs. Clinical guidelines have not kept up with the new developments.

Conclusion

The treatment of moderate-to-severe AD has changed dramatically with the approval of biologics and JAK inhibitors targeted at the underlying pathophysiology of this disease. With four agents already available and more to come, managed care has some challenges in steering cost-effective use of these agents.

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Evolving Considerations in Adolescent and Adult Immunizations: Best Practices for Immunizing in a COVID-19 Environment

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Summary

Vaccination is important for preventing disease and in the case of one vaccine, preventing cancer. Vaccines are not just for children but are also important for adolescents and adults. For most vaccines, concerted effort is needed to increase vaccination rates, especially given the challenges of the recent pandemic.

Key Points

- Vaccines are an important health intervention that saves lives.
- Vaccines are also cost-effective interventions.
- Clinicians and managed care can work together to identify those people who need recommended vaccines.

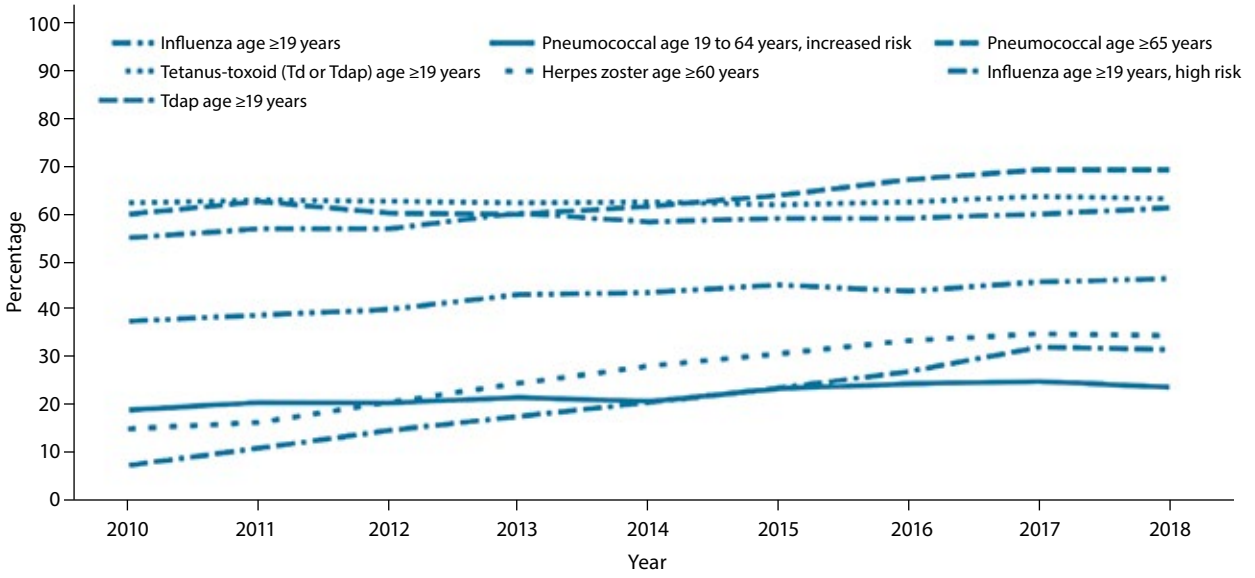
VACCINES ARE AN IMPORTANT HEALTH intervention. Routine childhood vaccination has been estimated to prevent approximately 42,000 deaths and 20 million cases of disease, averting an estimated $76 billion in total societal costs—in a single birth cohort alone.[1] This is three times more lives saved than seat belts and child restraints combined.[2] COVID-19 vaccinations alone were estimated to prevent 3.2 million deaths and 18.5 million hospitalizations in the United States (U.S.) from December 2020 through November 2022.[3]

COVID-19 also impacted the rate of routine vaccinations for children, adolescents, and adults due to shutdowns.[4] After many jurisdictions lifted stay at home orders, the number of vaccine doses administered during June to September 2020 approached pre-pandemic baseline levels, but did not increase to the level that would have been necessary to catch up children who did not receive routine vaccinations on time.[5] The drop in routine childhood vaccinations combined with lack of immune stimulation due to the reduced circulation of microbial agents during lockdown induced an "immunity debt" which appears to be having negative consequences in terms of high rates of influenza and respiratory syncytial virus (RSV) infections post shutdown. Even without the impact of a pandemic, vaccination rates in adults lag behind those for children. Exhibit 1 shows pre-pandemic rates over several years.[6]

Vaccine hesitancy has also grown recently, especially with regards to the COVID-19 vaccines and routine childhood vaccines. Managed care can work with clinicians to educate their members on how vaccines are evaluated for safety and how safety is continually monitored post-marketing through the Vaccine Adverse Events Reporting System (VAERS) and Vaccine Safety Data Link (VSD). In addition to education, clinicians can actively search for missed vaccines and seize opportunities for vaccination.

The Advisory Committee on Immunization Practices (ACIP) recommended vaccines for adults from 2022 are shown in Exhibit 2.[7] At the time of authoring this article, recommendations for 2023 were yet to be published. Of note, COVID-19

Exhibit 1: Adult Vaccine Coverage (Pre COVID-19)[6]



vaccination recommendations have not yet been incorporated into the ACIP overall vaccine guidelines. Selected vaccines recommended for adults and adolescents are spotlighted here including pneumococcal, human papilloma virus (HPV), herpes zoster, and influenza.

Over 90 different pneumococcal serotypes have been identified. Currently there are 13- and 15-valent pneumococcal conjugate vaccines (PSV-13, PSV-15), a 20-valent (PSV-20), and a 23-valent pneumococcal polysaccharide vaccine (PPSV-23). The PSV-13 vaccine is only recommended for use in children. During 2018 and 2019, the incidence of invasive pneumococcal disease (IPD) in adults aged 65 years and older was 24 per 100,000 population, and PCV-13 serotypes accounted for 27 percent of cases; additional serotypes unique to PCV-15, PCV-20, and PPSV-23 caused 15 percent, 27 percent, and 35 percent of IPD, respectively. In adults aged 19 to 64 years with certain underlying conditions, PCV-13 serotypes accounted for 30 percent of IPD; serotypes unique to PCV-15, PCV-20, and PPSV-23 caused 13 percent, 28 percent, and 43 percent of IPD, respectively. The recommendations for who should receive pneumococcal vaccination depends on risk and varies by age and underlying medical conditions. Either PCV-20 alone or PCV-15 in series with PPSV-23 is recommended for all adults aged 65 years and older, and for adults aged 19 to 64 years with certain underlying medical conditions or other risk factors who have not previously received a PCV vaccine or whose previous vaccination history is unknown.[8]

The Centers for Disease Control and Prevention (CDC) has assessed cost effectiveness of the current pneumococcal recommendations.[8] PCV-20 alone for all adults aged 65 and older had an estimated cost effectiveness from "cost-saving" to $39,000 per quality adjusted life year (QALY) gained. Two models assessed PCV-15 in series with PPSV-23 for all adults aged 65 and older with estimates ranging from "cost-saving" to $282,000 per QALY gained. Cost estimates for adults aged 19 to 64 with certain underlying medical conditions ranged from $11,000 to $292,000 per QALY gained for PCV-20 and $250,000 to $656,000 for PCV-15 in series with PPSV-23. The 2022 recommendations simplified adult pneumococcal vaccine recommendations and are expected to improve vaccine coverage among adults and prevent more pneumococcal disease.

The HPV vaccine is the first cancer prevention vaccine. HPV infection with oncogenic subtypes is responsible for more than 90 percent of anal and cervical cancers, 70 percent of vaginal and vulvar cancers, 60 percent of penile cancers, and 70 percent of oropharyngeal cancers.[9-11] HPV infection is the most common sexually transmitted infection in the U.S., with an estimated 24 million active cases and 5.5 million new cases each year.[12] The HPV vaccine has been shown to substantially reduce the risk of invasive cervical cancer especially when given prior to age 17 (Exhibit 3).[13] In 2007, Australia was one of

Exhibit 2: Recommended Adult Immunization Schedule by Age Group, United States 2022[7]

Vaccine	19 to 26 years	27 to 49 years	50 to 64 years	≥ 65 years
Influenza inactivated (IIV) or Influenza recombinant (RIV4) or Influenza live, attenuated (LAIV4)	1 dose annually; or **1 dose annually**			
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap each pregnancy; 1 dose Td/Tdap for wound management; 1 dose Tdap, then Td or Tdap booster every 10 years			
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)			
Varicella (VAR)	2 doses (if born in 1980 or later)	2 doses		
Zoster recombinant (RZV)	2 doses for immunocompromising conditions (see notes)		2 doses	
Human papillomavirus (HPV)	2 or 3 doses depending on age at initial vaccination or condition	27 through 45 years		
Pneumococcal (PCV15, PCV20, PPSV23)	1 dose PCV 15 followed by PPSV23 OR 1 dose (PCV20 (see notes)			1 dose PCV 15 followed by PPSV23 or 1 dose PCV20
Hepatitis A (HepA)	2 or 3 doses depending on vaccine			
Hepatitis B (HepB)	2, 3 or 4 doses depending on vaccine or condition		2, 3 or 4 doses depending on vaccine or condition	
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication, see notes for booster recommendations			
Meningococcal B (MenB)	19 through 23 years	2 or 3 doses depending on vaccine and indication see notes for booster recommendations		
Haemophilus influenzae type b (Hib)	1 to 3 doses depending on indication			

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection.

Recommended vaccination for adults with a additional risk factor or another indication.

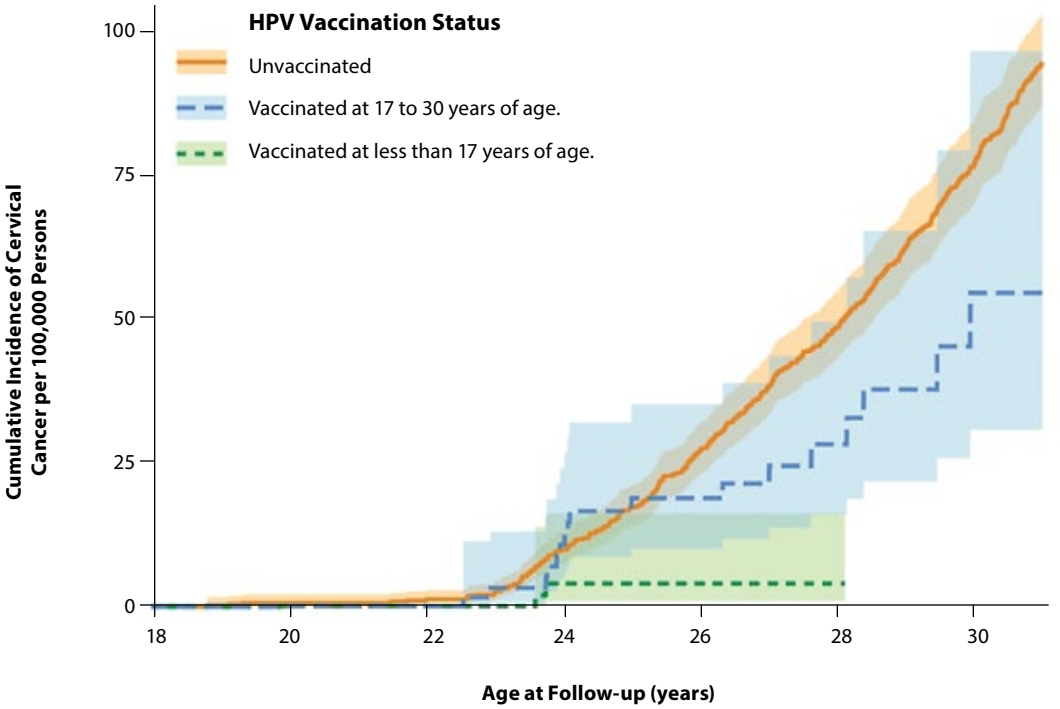
Recommended vaccination based on shared clinical decision-making.

No recommendations or not applicable

the first countries to introduce an HPV vaccination program and has since achieved high vaccination coverage across both men and women. A modeling study found that if high-coverage vaccination and recommended HPV screening is maintained, at an elimination threshold of four new cases per 100,000 women annually, cervical cancer could be considered to be eliminated as a public health problem in Australia within the next 20 years.[14]

The 9-valent recombinant vaccine (Gardasil® 9), which replaced an earlier 4-valent version, is FDA approved for females 9 through 45 years of age for the prevention of cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58, cervical, vulvar, vaginal, and anal precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, and genital warts caused by HPV types 6 and 11. It is also FDA-approved for males 9 through 45 years of age for the prevention

Exhibit 3: Impact of HPV Vaccination on Invasive Cervical Cancer[13]



of anal, oropharyngeal and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52, 58, anal precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58, and genital warts caused by HPV types 6 and 11.

The ideal time to vaccinate against HPV is prior to any exposure through sexual contact; HPV vaccination is recommended at ages 11 to 12 years.[15] Catch-up HPV vaccination is recommended for all persons through age 26 who are not adequately vaccinated. Some adults ages 27 through 45 years may decide to get the HPV vaccine based on discussion with their clinician, if they did not get adequately vaccinated when they were younger.

Unfortunately, the U.S. needs to continue to improve HPV vaccination rates. Coverage among adolescents with one or more doses of HPV vaccine increased from 71.5 percent in 2019 to 75.1 percent in 2020.[16] The percentage of adolescents who were up-to-date with HPV vaccinations increased from 54.2 percent in 2019 to 58.6 percent in 2020. Parental concerns about long-term safety, adverse events, age of child, and feeling their child is not at risk of an HPV-related disease are the primary reasons for parents avoiding having their adolescents vaccinated.[17,18] Clinicians and managed care should address parent concerns about safety and necessity to improve vaccination rates.

The cost-effectiveness ratio for adolescent HPV vaccination has been estimated to range from "cost-saving" to approximately $35,000 per QALY.[15] Avoidance of cancer care costs improves cost effectiveness. Catch-up vaccination of teenagers and young adults, applying more recent cancer costs, reduced the estimated cost per QALY gained by about $12,400.[19] Expanding vaccination to adults through age 45 years produces less favorable cost-effectiveness ratios.

Zoster vaccine recombinant (Shingrix®, RVZ) is recommended for the prevention of herpes zoster and related complications for immunocompetent adults aged 50 and older.[20] RZV is also recommended for immunocompetent adults who previously received live attenuated vaccine (Zostavax®) which was discontinued in 2020. Adults with a history of herpes zoster should also receive RZV. The two-dose regimen is 97 percent effective in preventing zoster in 50- to 69- year-olds and 91 percent in the 70 years and older population.[20] For preventing post-herpetic neuralgia, it is 91 percent effective in the younger

age group and 89 percent in those aged over 70. Protection remains high (more than 85%) in people 70 years and above four years following vaccination. The estimated cost of RZV is $31,000 per QALY for immunocompetent adults aged 50 and older. The number needed to treat-to-prevent one case of herpes zoster is 11 to 17 and to prevent one case of postherpetic neuralgia is 70 to 187.

Two doses of RZV are now recommended for immunocompromised people.[21] Effectiveness at preventing zoster is 68 percent in those with stem cell transplants and 87.2 percent in hematologic malignancies. Adverse event rates in immunocompromised patients are comparable to placebo. Vaccination is cost saving in stem cell transplants with a number needed to treat of 9 and vaccination in other immunocompromising conditions costs less than $99,000 per QALY.

Routine annual influenza vaccination is recommended for all persons aged six months and older who do not have contraindications, however, a vaccine appropriate for age and health status should be used.[22] For the 2022–23 flu season, there are three flu vaccines which are preferentially recommended for people 65 years and older—Fluzone High-Dose Quadrivalent vaccine, Flublok Quadrivalent recombinant flu vaccine and Fluad Quadrivalent adjuvanted flu vaccine. For most people who need only one dose for the season, September and October are generally the best times to be vaccinated. While ideally, it is recommended to vaccinate by the end of October, it is important to know that vaccination after October can still provide protection during the peak of flu season.

For the 2021–22 flu season, the overall cumulative hospitalization rate was 167.5 per 100,000 population with the highest rate among adults aged 65 years and older (50.8), followed by children aged 0 to 4 years (21.9), adults aged 50 to 64 years (16.2), children aged 5 to 17 years (9.0) and adults aged 18 to 49 (9.1).[23] The majority (96.7%) of influenza-associated hospitalizations, were due to influenza A viruses (99.2% of those subtyped were H3N2 viruses). Among those with information about underlying conditions, 93.7 percent of adults and 65.3 percent of children reported at least one underlying medical condition. The CDC estimated that about 5,000 people died from flu in the U.S. during the 2021–22 season.[23]

There is room to improved influenza vaccination rates. Coverage was 57.8 percent among children aged 6 months through 17 years, a decrease of 0.8 percentage points from the 2020–21 flu season, and flu vaccination coverage among adults 18 years and older was 49.4 percent, also a decrease of 0.8 percentage points from the prior season.[24] Half of all people aged 6 months and older (51.4%) were vaccinated during the 2021–22 season, a decrease of 0.7 percentage points from the prior season. Data on the 2022–23 season are not yet available.

Conclusion

Vaccines are among the most important public health initiatives. Unfortunately, vaccine use dropped during the COVID 19 pandemic. Additionally, vaccine hesitancy has been increasing. Payers and clinicians need to re-focus efforts on adolescent and adult vaccines to boost rates. Payers and providers will need to make joint efforts to educate, eliminate misunderstandings, and encourage patients to resume immunizations.

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Optimizing Management Decisions in Insomnia: Evidence-based Treatments to Improve Outcomes

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

Summary

Insomnia is a prevalent condition and significantly impacts patient health and well-being. Management of insomnia can be accomplished with cognitive behavior therapy and medications. Identifying and treating comorbidities which may be causing or worsening sleep issues is another important part of treatment.

Key Points

- Insomnia is very common and has major consequences.
- Insomnia can be directly managed by cognitive behavioral therapy and pharmacological agents.

INSOMNIA IS A COMMON SLEEP PROBLEM for adults. An estimated 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.[1,2] There is up to a 50 percent prevalence in clinical practices.

The negative outcomes of insomnia are substantial (Exhibit 1).[3-8] Individuals with insomnia exhibit performance impairments for several cognitive functions, including working memory, episodic memory, and some aspects of executive functioning.

Despite high rates of insomnia and significant consequences, few patients report being asked about sleep by their doctors. In 2005, only 29 percent of people reported being asked.[9] The biggest barrier that physicians identify in treating sleep disturbances is a poor understanding of insomnia and its treatment. All patients should be screened for sleep issues at annual visits and at follow-up visits for diabetes, hypertension, high cholesterol, obesity, and psychiatric issues.[10]

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, and/or early morning awakening with inability to return to sleep.[11] The sleep disturbance has to cause clinically significant distress or impairments in social, occupational, educational, academic, behavioral, and other important areas of functioning. It occurs at least three nights per week and is present for at least three months. Importantly, the sleep difficulty occurs despite adequate opportunity for sleep and cannot be explained by and does not occur exclusively during the course of another sleep-wake disorder. Insomnia should not be attributable to the physiological effects of a drug of abuse or medication and coexisting mental disorders. Medical conditions do not adequately explain the predominant complaint of insomnia.

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, obstructive 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. Some of the tools clinicians can use to aid in diagnosis are shown in Exhibit 2. A sleep

Exhibit 1: Consequences of Chronic Insomnia Disorder[3-8]

Impairments	Health Impact
• Fatigue or malaise	• Major depressive disorder
• Attention, concentration or memory impairments	• Increased risk of suicide
• Mood disturbance/irritability	• Hypertension
• Daytime sleepiness	• Myocardial infarction
• Concerns about, or dissatisfaction with, sleep	• Type 2 diabetes
• Behavioral problems (hyperactivity, impulsivity, aggression)	• Reduced quality of life
• Reduced motivation, energy or initiative	
• Proneness for errors and accidents	
• Reduced driving ability	
• Impaired social, family, occupational, academic performance	
• Increased work absenteeism and reduced productivity	
• Increased economic burden	

medicine consultation is suggested when obstructive sleep apnea syndrome, periodic limb movement disorder, narcolepsy, or other complicated sleep disorders are suspected, the patient exhibits violent behaviors or unusual parasomnias related to sleep, severe daytime sleepiness is present, or insomnia fails to respond to behavioral and/or pharmacologic therapy after an appropriate interval.

Treatment approaches include addressing the comorbid condition with specific treatments, directly treating the insomnia disorder, or simultaneously treat 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, mood stabilizers for mania, and medication change for iatrogenic insomnia. An example would be scheduling diuretic medication in the morning instead of evening so sleep is less likely to be affected. Directly treating the insomnia disorder can be with cognitive behavioral therapy (CBT), pharmacological agents, or both. Ideally both are used.

CBT combines restriction of time in bed, stimulus control and sleep hygiene education with cognitive therapy.[12,13] Restriction of time in bed is only staying in bed while actually asleep and is also called sleep restriction. Stimulus control refers to getting out of bed if unable to fall asleep within 20 minutes to do a boring activity before attempting sleep again. Sleep hygiene interventions such as having a quiet, dark sleeping area and avoiding stimulants are easy for patients to institute and can help improve sleep and the sleep environment. 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 minutes, awake after sleep onset was improved by 26 minutes, total sleep time was improved by 7.61 minutes, and sleep efficiency was improved by 9.91 percent.[14] 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. Primary care clinicians may not consider CBT due to lack of knowledge about CBT, its effectiveness, treatment beliefs, and lack of motivation because prescribing a medication is much easier. A major barrier for patients is limited or no insurance reimbursement for CBT.

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, alcohol, and many other alternative medications of questionable value.[15] The evidence for efficacy

Exhibit 2: Insomnia Diagnostic Tools

Procedure	Indications
History and physical exam	All
Epworth Sleepiness Scale	Daytime sleepiness
Fatigue Severity Scale	Fatigue
Insomnia Severity Scale	Insomnia screening and severity assessment
Actigraphy, sleep logs	Sleep pattern across time, circadian rhythm sleep disorders
Blood tests	Identification of comorbidities, ferritin (if restless leg syndrome suspected)
Home sleep testing	Obstructive sleep apnea
In-lab (attended) nocturnal polysomnography	Sleep apnea (obstructive, central), periodic limb movements in sleep, parasomnias (REM sleep behavior disorder), CPAP titration, seizures

for most of these is limited.[16] For some patients, antihistamines work fine for occasional use to get to sleep. The use of antihistamines for sleep among the elderly should be discouraged because the anticholinergic effects are associated with increased brain atrophy and dysfunction and clinical decline in older patients.[17] Melatonin is the most popular sleep supplement. 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).[18] The effects on sleep latency and sleep duration are magnified with sustained release products and higher doses. There are some concerns regarding possible adverse events with long-term use. Acute melatonin administration in humans has been shown to impair glucose tolerance but the effects of chronic use are unknown.[19]

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 but 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 are also present. Disadvantages including those not being well investigated in insomnia are, adverse events of daytime sedation, anticholinergic effects, weight gain, hyperglycemia, lipid abnormalities, risk of extrapyramidal symptoms and tardive dyskinesia.

Benzodiazepines approved for insomnia include triazolam, temazepam, estazolam, flurazepam, and quazepam which are all labeled for short-term use only and should not be used for chronic insomnia. The use of benzodiazepines in the treatment of insomnia is associated with an increase in sleep duration, but this is countered by a number of adverse events.

The benzodiazepine receptor agonists include zaleplon, zolpidem, and eszopiclone. 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. All of the benzodiazepines and benzodiazepine receptor agonists are DEA Schedule IV controlled substances based on potential for abuse.

Ramelteon is a melatonin receptor agonist that has been shown to decrease sleep latency. A low-

Exhibit 3: Adverse Effects of Hypnotics[22-25]

• *Benzodiazepine receptor agonists*	• *H1 receptor antagonist*
• Daytime sedation, psychomotor and cognitive impairment (depending on dose and half-life)	• Somnolence/sedation
• Rebound insomnia	• Nausea
• Respiratory depression in vulnerable populations	• *Orexin receptor antagonists*
• DEA Schedule IV	• Somnolence
• *Melatonin receptor agonist*	• Risk of impaired alertness and motor coordination, including impaired driving; narcolepsy symptoms; compromised respiratory function. Contraindicated in narcolepsy
• Headache, somnolence, fatigue, dizziness	• DEA Schedule IV
• Not recommended for use with fluvoxamine due to CYP 1A2 interaction	

Exhibit 4: Using Clinical Characteristics to Inform Treatment Decisions[25-28]

Age • Some therapies are better studied than others	**Comorbid mild-to-moderate OSA** • Ramelteon, suvorexant, daridorexant (lemborexant in mild OSA)
Sleep onset insomnia • Doxepin low dose • Zolpidem low dose sublingual as needed for middle of night awakening	**Comorbid mild-to-moderate COPD** • Ramelteon, suvorexant, daridorexant
Onset and maintenance insomnia • Eszopiclone, zolpidem ER, suvorexant, lemborexant, daridorexant	**History of substance use/abuse** • Ramelteon, doxepin
Need to awaken to auditory stimulus (parent with a baby, overnight on call) • Doxepin low dose, lemborexant, suvorexant	**Patient preference** **Cost**

dose formulation of doxepin, an antidepressant, which is a histamine 1 receptor antagonist, is FDA approved for treating insomnia and decreases time awake during the night. Doxepin and ramelteon are the only hypnotics which are not Schedule IV controlled agents.

The newest hypnotics target orexins, neuropeptides that regulate arousal, wakefulness, and appetite. Elevated plasma orexin-A levels have been shown in insomnia disorder.[20] Blocking the binding of wake-promoting orexin A and orexin B to receptors OX1R and OX2R is thought to suppress the wake drive. Suvorexant, lemborexant, and daridorexant are the three FDA-approved dual orexin receptor antagonists (DORA). They decrease sleep latency and time awake during the night, and increase total sleep time. All three are Schedule IV agents and are approved for onset and maintenance insomnia.

Adverse events of the prescription hypnotic agents are shown in Exhibit 3.[21-25] Patient populations vulnerable to adverse events from certain medications are those with respiratory compromise (COPD, obstructive sleep apnea), advanced age, history of substance use disorders, multiple sedating medication use, and hepatic impairment.

In choosing between pharmacotherapy or CBT, clinicians have several issues to consider. 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 a trained CBT therapist.[21] CBT is the first therapy of choice if there is chronic insomnia, a need for sustained clinical improvement, history of/or current substance use/abuse, multiple comorbid medical conditions, or chronic hypnotic use being discontinued.[22,23] Hypnotics 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. 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. Patient clinical characteristics that can be used to form treatment decisions are seen in Exhibit 4.[25-28]

Conclusion

Insomnia is highly prevalent in the community and in medical settings. It is associated with functional consequences and negative health outcomes. Clinicians need to perform a systematic evaluation and manage comorbidities whenever possible. Combinations of cognitive/behavioral strategies and pharmacological agents should be considered. A personalized approach matching patients' clinical characteristics with pharmacodynamic and pharmacokinetic features of medications should be developed.

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Evolving Treatment Strategies in the Management of Metastatic Melanoma: Optimizing Immunotherapy Approaches for Improved Outcomes

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Summary

Amazing progress in improving survival with metastatic melanoma has been made. Checkpoint immunotherapy, especially in combinations, has changed the prognosis from months to years. There is still a need for additional therapies for those who do not respond or progress on available agents.

Key Points

- Checkpoint immunotherapy as a single agent or combined immunotherapy is an option for all patients with metastatic melanoma.
- Combined immunotherapy is the preferred option for selected patients.
- Patients with BRAF-mutated tumors also have targeted therapy as an option but this is more likely to be used to reduce tumor burden for a short term before immunotherapy or after progression on immunotherapy.

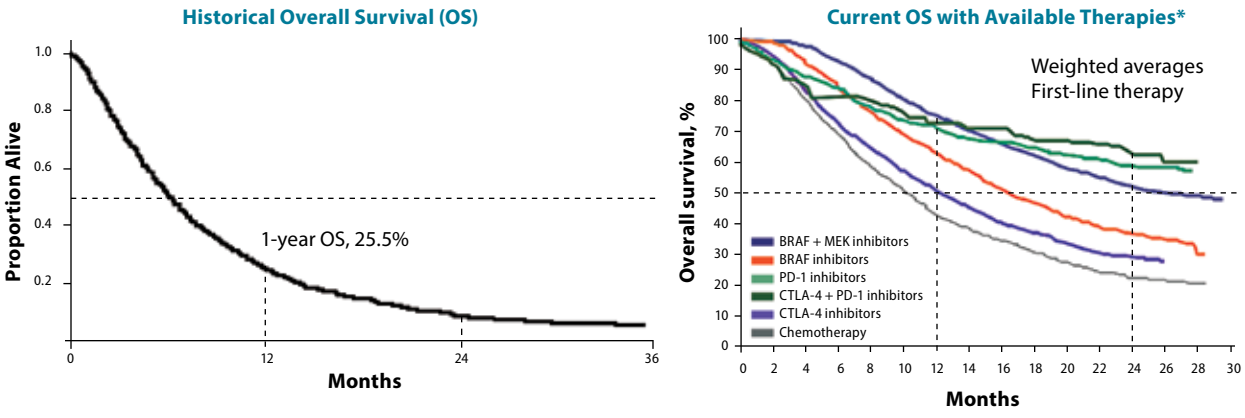
MELANOMA IS A RARE FORM OF SKIN cancer accounting for about 4 percent of skin cancers.[1] However, it is responsible for 90 percent of deaths due to skin cancer.[2] It is less common than non-melanoma skin cancers, however, it is much deadlier because of its propensity to metastasize. Cutaneous melanoma occurs anywhere on the skin but is most commonly located on the trunk.

In the United States (U.S.) there are approximately 75,000 cases yearly of which approximately 5 percent are metastatic at diagnosis.[3] Unlike other cancers, the incidence of melanoma is increasing. Between 2000 and 2009, the incidence climbed 1.9 percent annually. Dramatic changes in the treatment of metastatic melanoma since 2011 have made a significant impact on survival. Exhibit 1 compares historic survival to survival with newer targeted therapies.[4,5] There are now approximately 7,000 deaths annually in the U.S. compared to 10,000 a few years ago.

Once metastatic and unresectable, the treatment options for melanoma are checkpoint immunotherapy and targeted therapy provided specific genetic mutations are present. The programmed death one (PD-1) inhibitors (nivolumab, pembrolizumab) and nivolumab in combination with the CTLA-4 inhibitor ipilimumab or the lymphocyte-activation gene 3 (LAG-3) inhibitor relatlimab are the checkpoint immunotherapy used in metastatic melanoma. Targeted therapy includes BRAF (v-Raf murine sarcoma viral oncogene homolog B) and MEK (mitogen-activated protein kinase) inhibitor combinations in those patients with BRAF-mutated tumors.

LAG-3 and PD-1 are distinct inhibitory immune checkpoints that contribute to T-cell exhaustion. The

Exhibit 1: Survival Impact of Drug Development in Metastatic Melanoma[4,5]



* Exploratory analysis of survival data from 25 clinical trials representative of new treatment strategies in metastatic melanoma. Kaplan-Meier survival curves were grouped and compared by therapeutic strategy and treatment line.

newest approved therapy for metastatic melanoma is relatlimab which was FDA approved in March of 2022. It is a human IgG4 monoclonal antibody that binds to the LAG-3 receptor, blocks interaction with its ligands, including MHC II, and reduces LAG-3 pathway-mediated inhibition of the immune response. Antagonism of this pathway promotes T cell proliferation and cytokine secretion.

In the study used for FDA approval of relatlimab, the median progression-free survival (PFS) was 10.1 months with relatlimab-nivolumab as compared with 4.6 months with nivolumab (hazard ratio for progression or death, 0.75; $p = 0.006$ by the log-rank test).[6] Progression-free survival at 12 months was 47.7 percent with relatlimab-nivolumab as compared with 36.0 percent with nivolumab. Grade 3 or 4 treatment-related adverse events occurred in 18.9 percent of patients in the relatlimab-nivolumab group and in 9.7 percent of patients in the nivolumab group. Overall, this combination may provide a slightly better PFS with similar toxicity to nivolumab alone. This combination will likely replace some nivolumab use but not nivolumab/ipilimumab, for most patients, because of proven survival benefits with the nivolumab/ipilimumab. Nivolumab/relatlimab may be an option for patients with some high-risk features but who are risk adverse to try nivolumab/ipilimumab which causes a higher rate of Grade 3 and 4 adverse events (~50% versus ~20%).

The National Comprehensive Cancer Network (NCCN) preferred regimens for first-line treatment of Stage IV metastatic or unresectable disease are nivolumab and ipilimumab, nivolumab and relatlimab, pembrolizumab, or nivolumab.[7] All are category 1 recommendations. Other recommended regimens are combination targeted therapy if a BRAF V600-activating mutation is present. These include dabrafenib/trametinib, vemurafenib/cobimetinib, and encorafenib/binimetinib (all are category 1).

Considerations for using combination nivolumab/ipilimumab versus PD-1 monotherapy include a patient's willingness to take on a higher risk of treatment-related toxicities [immune-related adverse events (irAEs)], an absence of comorbidities or autoimmune processes that would elevate the risk of irAEs, and patient social support and preparedness to work with a medical team to handle toxicities.[7] Those patients who should be considered for nivolumab/ipilimumab are those with aggressive/advanced disease and good performance status, presence of BRAF-mutant disease, mucosal or acral primary, prior adjuvant PD-1 monotherapy, or progression on single agent PD-1.[7] The benefit of ipilimumab appears to be especially in those with BRAF-mutant disease. The 6.5-year overall survival (OS) rates were 57 percent with nivolumab/ipilimumab, 43 percent with nivolumab, and 25 percent with ipilimumab in patients with BRAF-mutant tumors and 46 percent, 42 percent, and 22 percent respectively in those with BRAF-wild-type tumors.[8] Single-agent immunotherapy is most appropriate for those with BRAF-wild-type disease, low-volume disease (M1a, M1b), history of an autoimmune disease, and risk-adverse patients. For example, a single mother with children still at home may not be willing or able to risk the adverse events of combination immunotherapy. The goals of the patient impacts treatment selection.

The sequencing trial DREAMseq found that in patients with treatment-naïve BRAF V600-mutant metastatic melanoma combination nivolumab/ipilimumab followed by BRAF and MEK inhibitor therapy, if necessary, should be the preferred treatment sequence because of a survival benefit.[9] Based on this trial and the survival data with combination immunotherapy, BRAF-targeted therapy is mostly as second-line therapy after progression on immunotherapy and in the adjuvant setting in the earlier stages of BRAF-mutant disease. The easy to manage toxicities, lack of long-term permanent adverse events such as adrenal insufficiency or type 1 diabetes, and oral administration provide advantages over immunotherapy in the adjuvant setting. Another use for BRAF-targeted therapy is to rapidly reduce symptomatic tumor burden before starting immunotherapy.

In choosing which BRAF/MEK combination to use, adverse events play a primary role because the three combinations have similar efficacy and cost. Vemurafenib/cobimetinib causes more rash, dabrafenib/trametinib more fevers, and encorafenib/binimetinib more nausea. Some data indicate that encorafenib/binimetinib is best tolerated. Additionally, it does not have the requirement to take on an empty stomach, which some patients appreciate. The adverse events of these agents are easier to manage than those of immunotherapy.

Triple therapy combining immunotherapy and BRAK/MEK inhibition for BRAF-mutant disease has also been evaluated. Addition of a PD-1 inhibitor to BRAF/MEK inhibition results in slight improvements in median PFS, PFS at one year, and duration of response, but no improvement in overall response. Triple therapy is associated with more clinical and financial toxicity. Atezolizumab [a programmed death ligand one (PD-L1) inhibitor] in combination with vemurafenib/cobimetinib does have an FDA-approved indication for use in BRAF-mutated metastatic melanoma based on statistically significant improvement of 12-month PFS (54% versus 45.1%). Ultimately, based on current data, it is hard to identify a patient population who should receive triple therapy versus sequenced immunotherapy then targeted therapy at progression.

Overall, the benefits of immunotherapy are huge for managing melanoma. Metastatic melanoma is becoming a chronic disease; however, patients are living good lives with Stage IV disease and are even returning to work. Many patients have long-term survival (10 or more years). These survival benefits have benefit for society, especially when younger people with metastatic disease can continue living. The downside of immunotherapy is that many more patients are being treated with expensive immunotherapy with potentially life-long adverse events as these therapies have moved to earlier stages. Immunotherapy as adjuvant therapy is an option depending on risk of recurrence after surgical removal as early as Stage II disease. The duration of treatment in the metastatic setting is likely longer than needed and not well defined. The duration of treatment which provides the best long-term survival needs to been defined. Currently, even if a patient gets a complete response, they continue to receive therapy for a year or more. There are patients who having been receiving immunotherapy for five to ten years and are reluctant to stop therapy because their disease is under control. A shorter duration of treatment in those with a complete response will improve patient quality of life and reduce costs.

PD-1 inhibitor refractory disease is an area where new therapies are needed. Lifileucel is an investigational tumor-infiltrating lymphocyte (TIL) treatment for use in patients with unresectable or metastatic melanoma whose disease has progressed on or after prior anti-PD-1 or PD-L1 therapy and targeted BRAF/MEK inhibitor therapy. Currently, there are no FDA-approved therapies in this patient population. The FDA has delayed a biologics license application for lifileucel until sometime in 2023 due to a request for additional data on the agent.[10] In August 2022, a rolling submission for lifileucel was initiated to the FDA based on findings of the Phase Trial (NCT02360579). In a presentation on the trial at the Society for Immunotherapy of Cancer (SITC) Annual Meeting in November 2022, data showed clinically meaningful and durable activity with lifileucel.[11] The overall response rate was 31 percent with eight complete responses and 40 partial responses and the median duration of response was not reached. Among responses, 42 percent extended beyond 18 months, and 40 percent of responses were ongoing at the median follow-up of the study at 27.6 months. In patients who achieved a response at their first assessment, the median OS was 13.9 months which had not been reached. Several trials of this agent alone and in combination with immunotherapy are ongoing.

Conclusion

Despite increasing financial burden, treatments have led to a dramatic improvement in long-term survival in patients with metastatic disease. Drivers of high costs are long-term treatment (likely unnecessary with immunotherapy) and increasing use in lower-risk patients. Defining an ideal treatment duration of immunotherapy will be one way to manage costs.

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Innovations in Prostate Cancer Management: Taking a Personalized Approach to Optimal Treatment

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Summary

The treatment of prostate cancer, especially metastatic disease, is becoming more personalized. Genomics and prostate specific imaging are being used to select targeted therapies. To optimize outcomes, a multidisciplinary approach should be used.

Key Points

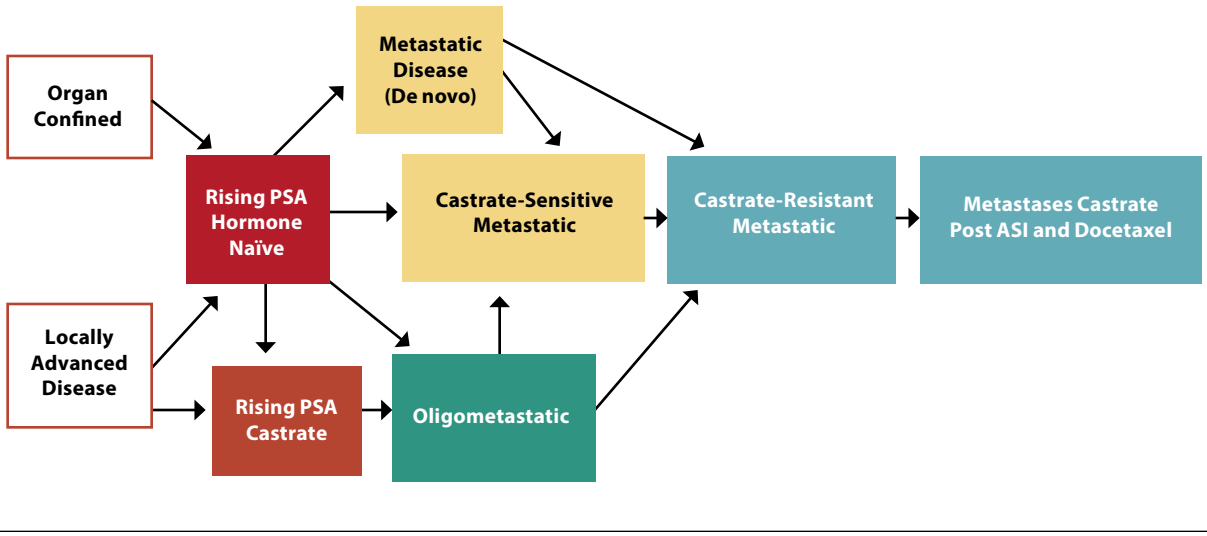
- Prostate cancer is an extremely heterogenous disease in its biology and clinical manifestations.
- Next generation imaging's impact will be significant and challenging given the limited prospective evidence to guide disease management.
- The movement of therapies into earlier stages of disease complicates advanced disease management.
- Optimal management of patients is not specialty dependent; it is expertise dependent.

PROSTATE CANCER, ESPECIALLY ADVANCED disease, is a complex and an extremely heterogenous disease managed by a variety of clinicians including community urologists, academic urologists, urologists in large urology group practices, medical oncologists, urologic medical oncologists, and radiation oncologists. In the absence of clear data supporting therapy sequence, the type of clinician patients see will likely impact what treatment they receive. Some innovations in prostate cancer management, which are impacting care, include next generation imaging, androgen deprivation therapy (ADT) intensification in non-metastatic castrate-resistant disease, a new radiopharmaceutical, and prostate cancer genomics.

Exhibit 1 shows the clinical states of prostate cancer across the spectrum of disease.[1] It is important to understand that each of these states are different and respond to treatment differently; there is also significant heterogeneity within each state. Some additional definitions are important. Prostate cancer with biochemical failure is a detectable, rising prostate specific antigen (PSA) and post-definitive local therapy. Non-metastatic castration-resistant prostate cancer (nmCRPC) has no evidence of metastatic disease on imaging, testosterone ≤ 50 ng/dL, and rising PSA. Castration-sensitive metastatic prostate cancer (CSMPC) is metastatic disease on imaging and non-castrate testosterone. Metastatic castration-resistant prostate cancer (mCRPC) is metastatic disease on imaging, testosterone ≤ 50 ng/dL, and rising PSA or new metastases on imaging.

Most cases of prostate cancer are diagnosed and treated while the disease is localized but some men will have metastatic disease at presentation, and others develop disseminated disease after definitive treatment. Management of metastatic prostate cancer, which is not considered curable, has the goals

Exhibit 1: The Clinical States of Prostate Cancer[1]



ASI = androgen signaling inhibitor

of prolonging survival, minimizing complications, and maintaining quality of life.

One innovation affecting metastatic disease treatment is the use of second-generation androgen receptor antagonists (apalutamide, enzalutamide, darolutamide) for nmCRPC. These agents are also called androgen signaling inhibitors. These three agents have been shown to improve survival in this setting but will impact the selection of therapy in mCRPC when it develops.[2-4]

Importantly, the patients in studies that led to FDA approval had been treated previously with ADT for PSA elevation only (biochemical disease) which has prompted the castrate resistance. ADT for biochemical disease is controversial. The use of these agents for nmCRPC has been limited. With the new more specific imaging technique discussed later, it is likely that many of these patients may actually have metastatic disease.

Treatments for mCRPC include cytotoxics (docetaxel, cabazitaxel), androgen signaling inhibitors, Radium-223 for symptomatic bone metastases, Lutetium Lu 177 for prostate-specific membrane antigen (PSMA)-positive metastases, and for a small number of patients, immunotherapy (Sipuleucel-T for selected patients or pembrolizumab for tumors with microsatellite instability high or deficient mismatch repair) or poly ADP-ribose polymerase (PARP) inhibitors for tumors with homologous recombination repair (HRR) deficiency (Exhibit 2).[5] No data exists on the best sequencing of these agents partly because of heterogeneity of the disease and how prostate cancer is treated by so many different specialists. The choice of first-line treatment for mCRPC depends on many factors including, prior systemic treatments, site and extent of disease involvement, comorbidities, presence or absence of symptoms, and genomics.[5]

The new imaging technique for prostate cancer is prostate-specific membrane antigen-positron emission tomography (PSMA-PET). PSMA is a well-established, prostate tissue-restricted, cell membrane target.[6] PSMA can be overexpressed in metastatic prostate cancer relative to normal tissue and is present in more than 80 percent of men with metastatic disease.[7,8] The currently FDA-approved PSMA agents are F-18 piflufolastat (also known as F-18 DCFPyL) and Ga-68 PSMA-11. Because of the increased sensitivity and specificity of PSMA-PET for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the National Comprehensive Cancer Network (NCCN) Guidelines do not recommend that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective, front-line imaging tool for these patients.[5] It is important to note that all of the prostate cancer trials led to FDA approvals of therapeutics except for the newest radiopharmaceutical utilized conventional CT/bone scans. Earlier detection with this more sensitive imaging may not mean earlier therapeutic intervention is beneficial but may result in earlier

Exhibit 2: NCCN Guidelines – mCRPC[5]

No prior docetaxel/no prior novel hormone therapy	Prior novel hormone therapy/no prior docetaxel
• Preferred regimens	• Preferred regimens
Abiraterone (category 1)	Docetaxel (category 1)
Docetaxel (category 1)	• Useful in certain circumstances
Enzalutamide (category 1)	Olaparib for HRRm (category 1)
• Useful in certain circumstances	Radium-223 for symptomatic bone metastases (category 1)
Radium-223 for symptomatic bone metastases (category 1)	Rucaparib for BRCA mutation
Sipuleucel-T (category 1)	Sipuleucel-T
Prior docetaxel/no prior novel hormone therapy	**Prior docetaxel and prior novel hormone therapy**
• Preferred regimens	• Useful in certain circumstances
Abiraterone(category 1)	Lu-177–PSMA-617) for PSMA positive metastases (category 1)
Cabazitaxel	• Preferred regimens
Enzalutamide (category 1)	Cabazitaxel (category 1)
• Useful in certain circumstances	Docetaxel rechallenge
Radium-223 for symptomatic bone metastases (category 1)	• Useful in certain circumstances
Sipuleucel-T	Olaparib for HRRm (category 1)
	Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb
	Radium-223rrr for symptomatic bone metastases (category 1)
	Rucaparib for BRCA mutation

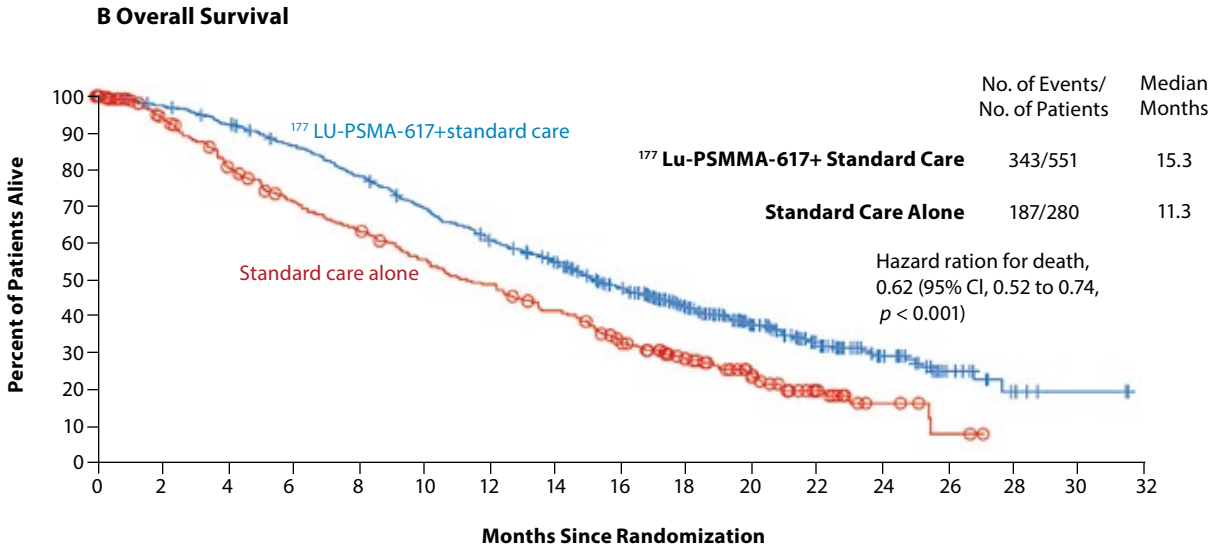
HRRm = homologous recombination repair mutation; MSI-H = microsatellite instability high;
dMMR = deficient mismatch repair; TMB = tumor mutational burden

intervention in any case. PSMA imaging is going to find many more metastatic cases than conventional imaging. Although there are some utility questions for now, it is the best way to assess patients because of specificity. Most major insurance carriers are now covering this test for selected patients.

Oligometastatic prostate cancer (OMPC) is one area where PSMA imaging will impact treatment. OMPC is generally defined as a limited number of metastatic sites on imaging (number not well defined, typically < 5) and represents a transitional state between localized clonal disease and widespread metastatic disease with a wide spectrum of disease biology and clinical behaviors. If the disease is treated when there are limited sites which are all of the same type (clones), it may be possible to cure metastatic disease. More sensitive disease detection with PSMA-PET may result in aborting planned curative intent therapies without data. Also, earlier detection may result in more therapy being given earlier than in the past with the potential for more toxicity without demonstrated benefit. There are trials examining targeted metastases-based treatments in oligometastatic disease and trying to identify the outcomes of importance. Outcomes in these trials include time to use of hormonal therapy, time to metastases, metastases-free survival, and overall survival. One problem with time to use of hormonal therapy as an outcome is when starting ADT is completely arbitrary. There is no defined time to start ADT outside the metastatic setting.

Over and under treatment is a consequence of next generation imaging. Other examples beyond OMPC where this might occur are locally advanced prostate cancer and biochemical failure. For a patient with locally advanced prostate cancer, multimodality therapy is the standard of care (surgery and radiation, radiation and hormone therapy, etc.) for cure. There is a concern that with PSMA-PET, based on some distant possible metastatic sites, a clinician may say *"we can't cure you so we will not try"*. For a patient with biochemical failure who, has never received ADT but PSMA-PET, shows a small area of disease, he is likely to get started on ADT, however, this would be about two years earlier than would have happened with conventional imaging (which would

Exhibit 3: Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer[13]



not have shown the small area of disease). While on ADT, the patient develops diabetes and heart disease which may be a consequence of the ADT and has a stroke and dies.

There is evolving impact of genomics in prostate cancer treatment. Testing should be offered to all patients with metastatic prostate cancer. Targetable mutations may be either germline or somatic (tumor) and somatic DNA testing results may change over time due to the genetic instability of tumor DNA and are identified by serial tumor or liquid biopsies.[9] Twenty-three percent of mCRPC have somatic DNA repair alterations and about 12 percent of men have germline HRR alterations such as BRCA mutations.[10] Those with a HRR gene mutation (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L) who have been treated previously with androgen receptor-directed therapy should receive a PARP inhibitor.[5] Immunotherapy with pembrolizumab is an option for those who have received prior docetaxel and androgen receptor-directed therapy and who have microsatellite high, deficient mismatch repair, or high tumor mutational burden.

The newest strategy is to combine PARP inhibition with ADT even if DNA repair mutations are not present. The combination of olaparib with abiraterone as first-line therapy in mCRPC regardless of HRR mutation status led to a 34 percent risk reduction of progression or death and 8.2 month improvement in imaging based progression-free survival (PFS).[11] Similar results were seen with the combination of niraparib and abiraterone which reduced risk of progression or death by 47 percent in those with BRCA 1 or 2 mutation.[12] Both trials report significant imaging based PFS benefit, but the overall survival data are still immature. Results from a combination trial with talazoparib are pending. The population studied (progression from ADT) in these trials is not the future state of mCRPC as more and more patients over time will have ADT intensification in the non-metastatic disease setting. Additionally, these studies do not address a key clinical/economic question of upfront combination versus sequenced therapy. These combinations may be recommended therapy in future but are not currently included in the NCCN Guidelines.[5]

The newest therapy for mCRPC is a radiopharmaceutical, lutetium Lu 177 vipivotide tetraxetan (Pluvicto®) which was FDA approved in February 2022. It is indicated for the treatment of adult patients with PSMA-positive mCRPC who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy. This treatment has an FDA-approved complementary diagnostic imaging agent, Locametz®, after radiolabeling with gallium-68 for the identification of PSMA-positive lesions. The active moiety, the radionuclide lutetium-177, is linked to a moiety that binds to PSMA. Upon binding to PSMA expressing cells, beta emission from lutetium-177 delivers

radiation to the cells, as well as to surrounding cells, and induces DNA damage which can lead to cell death. The trial that led to FDA approval found that lutetium Lu 177 vipivotide tetraxetan plus standard care compared to standard care significantly prolonged both imaging-based progression-free survival (median, 8.7 versus 3.4 months; $p < 0.001$) and overall survival (15.3 versus 11.3 months; $p < 0.001$; Exhibit 3).[13]

The NCCN Guidelines list this therapy as category 1 treatment option for patients with one or more PSMA-positive lesion and/or metastatic disease that is predominately PSMA-positive and with no dominant PSMA-negative metastatic lesions who have been treated previously with androgen receptor-directed therapy and a taxane-based chemotherapy.[5] The guidelines state that both Ga-68 PSMA-11 or F-18 piflufolastat PSMA imaging can be used to determine eligibility.

As previously noted, multiple specialties are involved in the care of patients during their disease course. Urology and radiation oncology have a close working relationship in localized/locally advanced disease. Advanced disease is managed by a variety of clinicians with varying levels of experience. Introduction of more complex and potentially toxic regimens such as ADT and PARP combination complicate issues as uptake among different clinical specialties will impact therapeutic decision making. Uptake of new data, imaging, genomics, and therapeutics is more optimal with interdisciplinary care which should be encouraged for prostate cancer management.

Conclusion

Prostate cancer is an extremely heterogenous disease in its biology and clinical manifestations. The impact of next generation imaging will be significant and challenging given the limited prospective evidence to guide management. The movement of therapies into earlier stages of disease complicates advanced disease management. Overall, optimal management of patients is not specialty dependent; it is expertise dependent.

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Improving the Treatment Outcomes in the Management of Psoriatic Arthritis

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Summary

Psoriatic arthritis (PsA) can be treated effectively with numerous agents that target the underlying pathology of this inflammatory disease. The available PsA specific agents reduce symptoms and inhibit joint damage which commonly occurs with this disease.

Key Points

- Treatment guidelines recommend selecting agents based on affected domains.
- A treat-to-target approach using a guideline-based treatment selection, shared decision making, and multidisciplinary management, can be used to improve patient outcomes.

PSORIATIC ARTHRITIS IS A PROGRESSIVE, erosive, chronic, heterogeneous, systemic inflammatory disease affecting six different clinical domains (Exhibit 1).[1] PsA presents in up to 30 percent of patients with psoriasis.

PsA has to be distinguished from rheumatoid arthritis (RA) and other common causes of joint pain. Joint involvement is typically, but not always, asymmetric in PsA, while it is predominantly symmetric in RA. Bone erosions, without new bone growth, and cervical spine involvement are distinctive of RA, while axial spine involvement, psoriasis and nail dystrophy are distinctive with PsA.[2] The majority of patients with PsA have seronegative test findings for rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) antibodies, while approximately 80 percent of patients with RA have positive findings. Although there is overlap in the pathogenesis of PsA and RA, differences are also present that affect the efficacy of treatment. In PsA, levels of interleukin (IL)-1β, IL-6, IL-17, IL-22, IL-23, interferon-γ and tumor necrosis factor-α (TNF-α) are elevated and are thus therapeutic targets.

Beyond the joints and skin, PsA also impacts various aspects of everyday life and causes whole body inflammation. Fatigue, poor sleep quality, physical function limitations, significant psychosocial burden, and diminished work capacity are all common.[3] Common comorbidities in PsA include ocular inflammation (uveitis/iritis), inflammatory bowel disease, and increased risk of cardiovascular disease.

It is important for dermatologists and others who care for patients with psoriasis (PsO) to recognize the potential for PsA. Nearly 52 percent of patients with PsO experience joint pain without a diagnosis of PsA.[1] PsA frequently develops within 10 years following the appearance of PsO. Eighty-five percent of patients develop PsO before PsA, but PsA may precede or occur concurrently. The median lag time from disease onset to a confirmatory diagnosis of PsA is 2.5 years.[4] An easy pneumonic for thinking about PsA is shown in Exhibit 2.[5] Early detection and treatment of PsA are critical for improving long-term patient outcomes and minimizing irreversible joint damage.

The diagnostic workup for PsA requires physical examination (nail changes, dactylitis), laboratory testing including markers of inflammation and autoimmunity, arthrocentesis and synovial fluid

Exhibit 1: Clinical Domains of PsA[1]

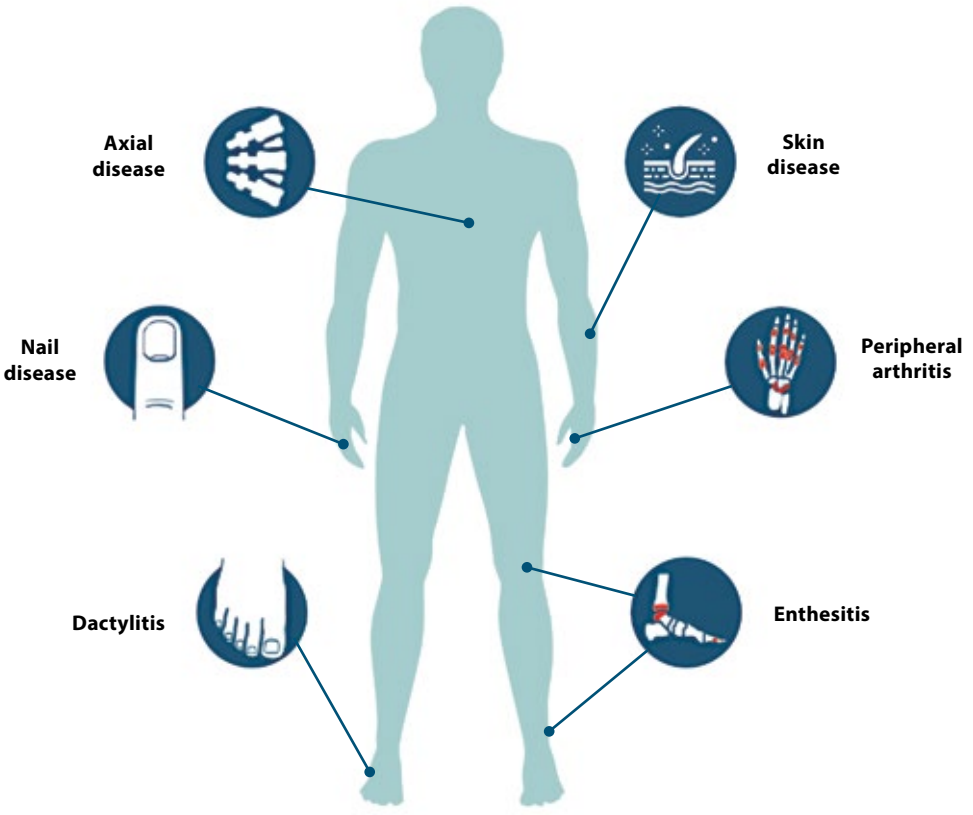


Exhibit 2: Clinical Diagnosis of PsA[5]

P	**P**ain in the joints
S	**S**tiffness > 30 minutes after inactivity **S**ausage digit (dactylitis)
A	**A**xial spine involvement, back pain associated with stiffness and pain that improves with activity

analysis, plus radiographs of involved joints (e.g., hands, feet, sacroiliac joints).

The goals of PsA treatment are to reduce pain, improve quality of life and function, and prevent structural damage and complications.[3] Achieving these goals requires management by a multidisciplinary team, engagement of patients as stakeholders in shared decision-making, and identification and consideration of comorbidities as they impact treatment selection. Besides comorbidities, various other factors affect treatment selection including disease severity, patient preferences, potential adverse events, treatment guidelines, and clinical evidence.

Numerous agents are available for treating PsA (Exhibit 3). Based on noncomparative studies, the

Exhibit 3: PsA Treatment Toolbox

Nonpharmacologic therapies	Physical therapy, occupational therapy, smoking cessation, weight loss, massage therapy, exercise
Symptomatic treatments	Nonsteroidal anti-inflammatory drugs, local glucocorticoid injections
Oral small molecule	Methotrexate*, sulfasalazine*, cyclosporine*, leflunomide*, apremilast
TNF inhibitor	Etanercept, infliximab, adalimumab, golimumab, certolizumab pegol
IL-12/23 inhibitor	Ustekinumab
IL-17 inhibitor	Secukinumab, ixekizumab
T cell costimulation modulator	Abatacept
JAK inhibitor	Tofacitinib, upadacitinib
IL-23 inhibitor	Guselkumab, risankizumab, tildrakizumab*

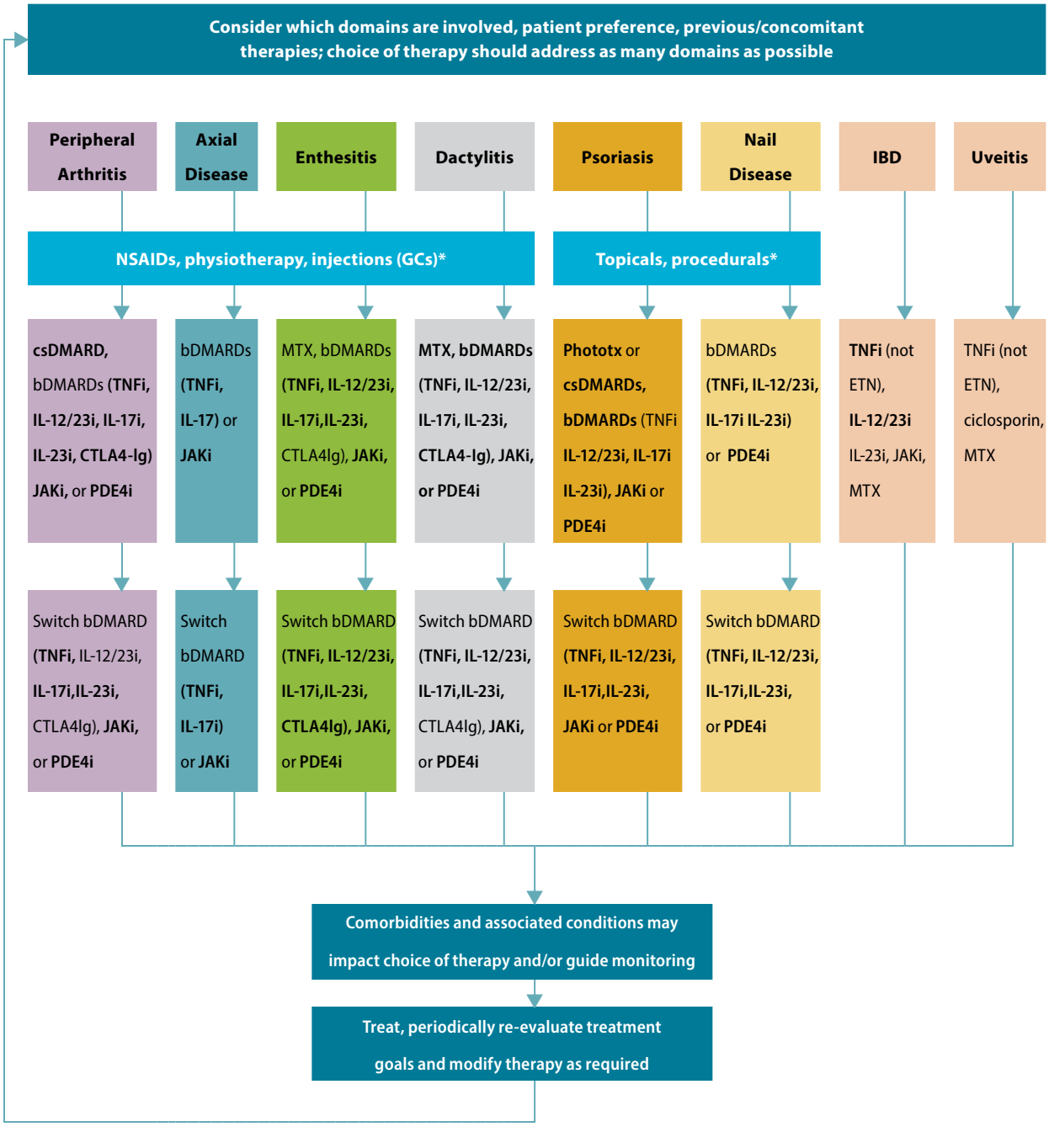
*Not FDA-approved for PsA
IL = interleukin; JAK = Janus kinase; TNF = tumor necrosis factor

biologics and Janus Kinase (JAK) inhibitors are more effective in reducing signs and symptoms based on American College of Rheumatology 20 percent improvement (ACR20) and in targeting selected domains affected by PsA than the older conventional disease-modifying agents. Treatment of PsA also inhibits joint damage. The 2018 American College of Rheumatology/National Psoriasis Foundation guidelines recommend starting therapy in active PsA with a TNF inhibitor.[6] If the disease is still active after a TNF inhibitor, the guidelines suggest switching to another TNF inhibitor, which has been shown not to be very effective, before moving to an interleukin 17 (IL-17) inhibitor and places the IL-12/23 and IL-23 inhibitors as options after failure of the IL-17 inhibitor. The 2021 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) guidelines recommend choosing therapy based on the affected domains and selected comorbidities such as inflammatory bowel disease which can be exacerbated by IL-17 inhibitors (Exhibit 4).[7] These guidelines provide more options for first-line therapy and recommend addressing as many affected domains as possible with the selected treatment. Efficacy of therapy can be assessed using minimal disease activity (MDA) criteria. A patient is classified as having MDA when he or she meets five of the following seven criteria: tender joint count ≤ 1, swollen joint count ≤ 1, psoriasis area and severity index (PASI) ≤ 1 or affected body surface area (BSA) ≤ 3 percent, patient pain on visual analogue scale (VAS) ≤ 15, patient global activity VAS ≤ 20, health assessment questionnaire (HAQ) ≤ 0.5, and tender entheseal points ≤ 1.[8] Tight control of PsA disease activity through a treat-to-target approach significantly improves joint outcomes for newly diagnosed patients, with no unexpected serious adverse events reported.[8]

Today's patients and their families want more than treatment; they want to be engaged in their care.[9] They want inclusion in personalized decision-making, education about their disease and treatment options, updates on progress of their care, and to be treated with respect and dignity throughout their disease journey. They want to be shown options for treatment and arrive at the decisions together. Principles of shared decision making are shown in Exhibit 5. Shared decision making can improve treatment satisfaction which is defined as the degree to which patients perceive that the treatment fulfills their health needs and is a reflection of the patient's experience with the therapeutic process, such as duration, outcomes, and benefit.[10] Treatment satisfaction is influenced by preferences, beliefs, and adherence. Dissatisfaction often results in nonadherence, which may be interpreted by providers as treatment failure.

Given the mounting number of therapeutic options and the complexity of management of PsA, the disease can be optimally treated by a multidisciplinary approach with a collaborative approach between rheumatologists, dermatologists, primary care, pharmacists, and other specialists.[11] The guidelines also recommend multidisciplinary management.[7]

Exhibit 4: GRAPPA PsA Treatment Recommendations 2021[7]



csDMARD = conventional synthetic DMARD (MTX, SSZ, LEF, CyA, unless otherwise specified); CyA = cyclosporin; CTLA4-Ig = abatacept; ETN = etanercept; GC = glucocorticoids; IA = intra- articular; IBD = inflammatory bowel disease; IL-12–IL-23i = IL-12–IL-23 inhibitor; IL-17i = IL-17 inhibitor; IL-23i = IL-23 inhibitor; JAKi = Janus kinase inhibitor; LEF = leflunomide; MTX = methotrexate; PDE4i = phosphodiesterase 4 inhibitor (apremilast); PsA = psoriatic arthritis; SIJ = sacroiliac joint; SSZ = sulfasalazine; TNFi = TNF inhibitor; UC = ulcerative colitis.
Bold text indicates a strong recommendation, standard text a conditional recommendation.
The asterisks indicate a conditional recommendation based on data from abstracts only.

Exhibit 5: Principles of Shared Decision-Making

- Create a supportive environment for open discussion.
- Clarify the timeline needed for the decision, including the opportunity to revisit at subsequent visits, and engage family or others as appropriate.
- Identify decision options and the outcomes affected by those options.
- Check the patient's understanding of everything involved in each option and outcome, and provide basic patient information as needed.
- Obtain evidence about the outcomes of different options, and translate the evidence to the individual patient's situation.
- Select the options and outcomes most relevant to the patient.
- Communicate the expected probabilities of different outcomes for the decision options.
- Engage the patient in a discussion of his/her values and preferences.
- Offer advice as the patient requests it to inform the decision.
- Support the patient in the selection of an option.

Conclusion

Psoriatic arthritis is an inflammatory disease associated with extra-articular manifestations, several comorbidities, reduced quality of life, and psychosocial burden. A treat-to-target approach using guideline-based treatment selection, shared decision making, and multidisciplinary management can be used to improve patient outcomes.

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Managed Care Perspectives on the Treatment and Management of Ovarian Cancer: Optimizing Outcomes with PARP Inhibitors

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Summary

The availability of poly (ADP-ribose) polymerase (PARP) inhibitors for maintenance and treatment of advanced ovarian cancer has led to significant changes in the treatment paradigm for this disease. Upfront maintenance therapy with PARP inhibitors, with or without bevacizumab, is reducing recurrences which will hopefully translate to continued improvements in overall survival.

Key Points

- Maximizing upfront outcomes depends on where patients receive treatment, who treats them, and how they are treated.
- Data support important clinical efficacy of PARP inhibitors for ovarian cancer in treatment and maintenance settings.
- Upfront maintenance is more commonly being used but overall survival data for this setting is pending.
- Patient counseling and adverse event management are key to successful PARP inhibitor outcomes.

THE AMERICAN CANCER SOCIETY ESTIMATES for ovarian cancer in the United States for 2023 are 19,710 new cases and 13,270 deaths.[1] Ovarian cancer ranks fifth in cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system. A woman's risk of getting ovarian cancer during her lifetime is about one in 78 and her lifetime chance of dying from ovarian cancer is about one in 108. Between 1975 and 2016, the five-year survival rate for ovarian cancer increased from 33 percent to 48 percent among non-Hispanic white women, but decreased from 44 percent to 41 percent in African American women. Data on survival with newer agents is not yet available.

Exhibit 1 shows the typical course for a woman with ovarian cancer. First-line treatment is surgery (primary or interval debulking) plus primary or neoadjuvant chemotherapy with carboplatin and paclitaxel. Previously, this was the only treatment but 70 to 80 percent of patients with advanced-stage disease will have recurrence. Now bevacizumab may be added to chemotherapy and/or a poly (ADP-ribose) polymerase (PARP) inhibitor for maintenance may be used to reduce risk of recurrence. With maintenance therapy, fewer patients are having recurrences and even some cures are now being seen.

A crucial unmet need is the development of new strategies that will ultimately improve the overall survival of patients with epithelial ovarian cancer (EOC). Despite high rates of complete response to the combination of tumor reductive surgery and adjuvant platinum-taxane-based chemotherapy,

Exhibit 1: Typical Course of Advanced Ovarian Cancer

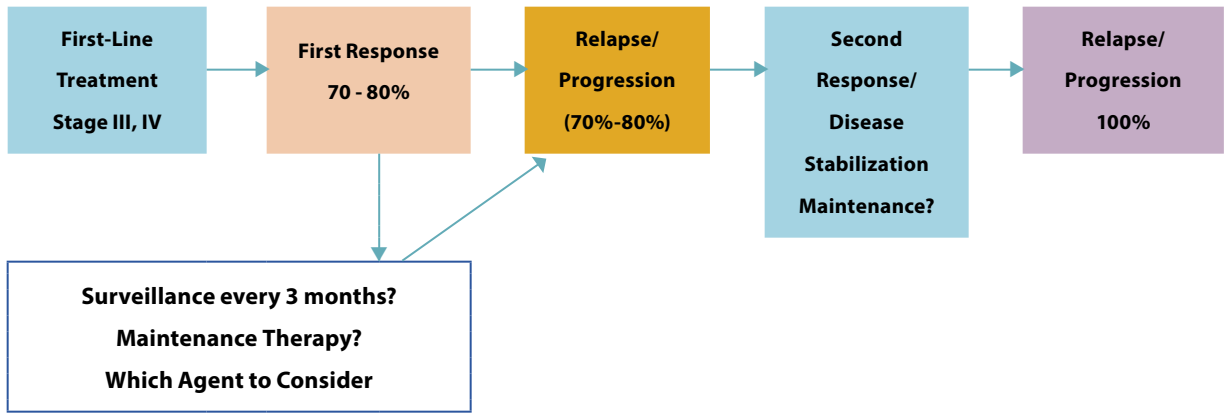

Exhibit 2: PARP Inhibitor Indications

Agent	Dose	Treatment Indication	Maintenance Indication
Olaparib	300mg BID (2 x 150mg capsules)	*gBRCA* mutant ovarian cancer ≥ 3 prior therapies	*BRCA* mutant ovarian cancer after response to upfront RX. HRD ovarian cancer after response to upfront RX in combination with bevacizumab. Platinum-sensitive ovarian cancer after response to platinum-based RX.
Rucaparib	600mg BID (2 x 300mg tablets)	*gBRCA/sBRCA* mutant ovarian cancer ≥ 2 prior therapies	Platinum-sensitive ovarian cancer after response to platinum-based RX.
Niraparib	300 mg QD (3 x 100mg capsules)	HRD ovarian cancer ≥ 3 prior therapies	Advanced ovarian cancer after response to upfront RX. Platinum-sensitive ovarian cancer after response to platinum-based RX.

gBRCA = germline breast cancer; sBRCA = somatic breast cancer; HRD = homologous recombination deficiency; RX = chemotherapy; QD = once daily; BID = twice daily

the vast majority of patients with Stage III/IV EOC recur with a median progression-free survival (PFS) of approximately 18 months. In those who recur, despite decades of clinical investigations, most cytotoxic and biological agents result in only modest rates of response and have a typical median PFS of three months. At relapse, the patient may have platinum-sensitive or resistant disease. Platinum-sensitive disease is considered progression at six or more months after completion of platinum-based chemotherapy and has a good prognosis. Platinum-resistant disease is an early progression after completion of platinum-based chemotherapy and has a poor prognosis. At recurrence, ovarian cancer is considered incurable. Thus, the goal of treatment is to achieve more cures with upfront treatment so patients can live longer better lives.

Maximizing upfront outcomes depends on where patients receive treatment, who treats them, and how they are treated. High-volume treatment centers with multidisciplinary resources and high-volume physicians with surgical expertise are associated with superior treatment and survival outcomes.[2,3] Many patients in underserved racial groups and

with lower socioeconomic status mostly receive treatment in low-volume centers. All patients should be genomic tested at diagnosis to steer treatment decisions but this is not occurring; only about 30 percent of those with newly diagnosed disease are being tested.[4] Lower testing rates are again seen in certain racial and socioeconomic groups.

PARP inhibitors are the newest treatment for ovarian cancer. DNA single-strand breaks (SSBs) occur frequently in cells and PARP detects and repairs them. If PARP is blocked, during the cell replication process unrepaired SSBs are converted into double-strand breaks (DSBs). Normal cells can repair DSBs with homologous recombination. Cancer cells with homologous recombination deficiency (HRD) from a BRCA or other HRD mutation in the presence of PARP inhibition have no avenue to repair breaks in DNA, thus blocking PARP leads to cell death.

Three PARP inhibitors are currently approved for both treatment and maintenance of ovarian cancer (Exhibit 2). These agents were first studied in and indicated for later-line treatment (third-line or later). Subsequently, they were studied for maintenance after treatment for a platinum sensitive recurrence. They are approved for all patients with platinum response for second-line maintenance; HRD mutations are not necessary for efficacy. Using PARP inhibitors earlier as second-line maintenance rather than reserving them for later-line treatment is important for improving overall survival (OS). The best chance of response with second-line maintenance is in those with BRCA or other HRD mutations but there is modest benefit in those without these mutations. For example, with rucaparib, PFS was 11.2 months better than placebo with a BRCA mutation, 8.2 months with HRD, and 5.4 months with no mutations.[5]

The next iteration of therapy was to study these agents as maintenance after first-line therapy for which olaparib and niraparib are now approved. Using olaparib in this setting in BRCA-mutation positive patients led to a 70 percent reduction in risk of progression and the benefits continue even after patients stop taking two years of maintenance.[6] In a high risk for recurrence population, niraparib provided a clinically significant benefit in the HR-proficient subgroup with a 32 percent risk reduction in progression or death in addition to significant benefits in HRD subgroups.[7] Again there is more benefit with maintenance after first-line therapy rather than waiting to use a PARP inhibitor in later lines of therapy and the most benefit occurs in BRCA or HRD mutation.

Another iteration of therapy is the combination of olaparib with bevacizumab as first-line maintenance after treatment with chemotherapy and bevacizumab. This combination improves PFS by 5.6 months over bevacizumab alone.[8] The most benefit was in those with BRCA or HRD mutation. Thus, not all patients necessarily need a PARP inhibitor added to bevacizumab maintenance but those with the mutations should. The benefit of stopping bevacizumab at the end of chemotherapy and only using a PARP inhibitor in those with mutations has not been addressed in any study. The current standard of care is the use of PARP inhibitors in the first-line maintenance setting. Because it is standard of care to consider these agents after initial therapy, universal genomic testing at diagnosis is important for all patients to help the clinician and patient reach a shared decision after weighing the risks and benefits of maintenance therapy.

Toxicity and efficacy are similar across the board with PARP inhibitors for either treatment or maintenance. In the maintenance setting, these agents actually improve quality of life.[9,10] Given comparable efficacy of the three agents available for ovarian cancer treatment, other characteristics will inform choice, such as toxicities, drug-on-drug interactions, dosing schedule (BID versus niraparib QD), price (copays), and special clinical situations. For example, rucaparib causes more hepatologic adverse events, niraparib more hypertension and bone marrow suppression, and olaparib more neutropenia. Olaparib and talazoparib doses need adjustment for renal dysfunction. Niraparib has no known drug-on-drug interactions but interactions can be managed with others. Some patients may prefer once-a-day dosing with niraparib compared to twice-a-day dosing for olaparib and rucaparib. An example of a special clinical situation for choosing therapy is treatment of central nervous system metastases. Talazoparib is not FDA indicated for ovarian cancer but it crosses the blood-brain barrier and is effective for brain metastases.

Even though PARP inhibitors are "just a pill", there are adverse events but most are manageable. It is important to manage expectations of patients and caregivers to alleviate key symptoms so that therapy can continue uninterrupted. Counseling on the possible adverse events and how to manage them is important. Monitoring for adverse events should be at least once-a-month during the first few cycles of therapy. When starting therapy, clinicians should consider weekly nurse visits for symptom, vitals, and laboratory monitoring. Prophylactic therapy for nausea is important; PARP inhibitors are considered moderately emetogenic. There is an increased risk of myelosuppression in heavily pre-treated patients. Patients don't have to start on the PARP inhibitor

immediately after finishing chemotherapy; a recovery period is acceptable and may improve tolerance. There is no increased toxicity in patients with BRCA mutation. If Grade 3 or 4 toxicity occurs, dose reductions and holding therapy probably may well be necessary.

Overall, several things are key to maximizing patient outcomes with PARP inhibitors. Clinicians need to prepare the patient for possible adverse events and how to manage those. Multidisciplinary resources can be helpful for identifying and managing adverse events and for enhancing therapy adherence. Frequent contact with patients is important.

Conclusion

Disparities exist in genomic testing and treatment of ovarian cancer that have a clear impact on clinical outcomes. Data support important clinical efficacy of PARP inhibitors in ovarian cancer in the treatment and maintenance settings. Upfront maintenance is more commonly being used but overall survival data for this setting is pending. Patient counseling is key to successful PARP inhibitor outcomes. Adverse events are common but manageable and quality of life actually improves on therapy. Incorporating multidisciplinary resources into education and support can help keep patients on therapy.

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Notes

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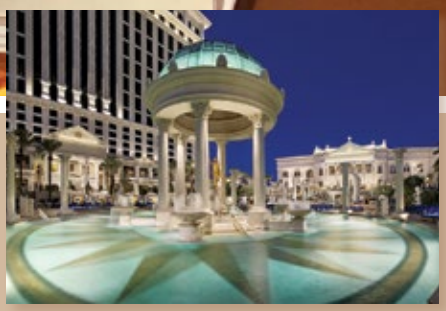

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