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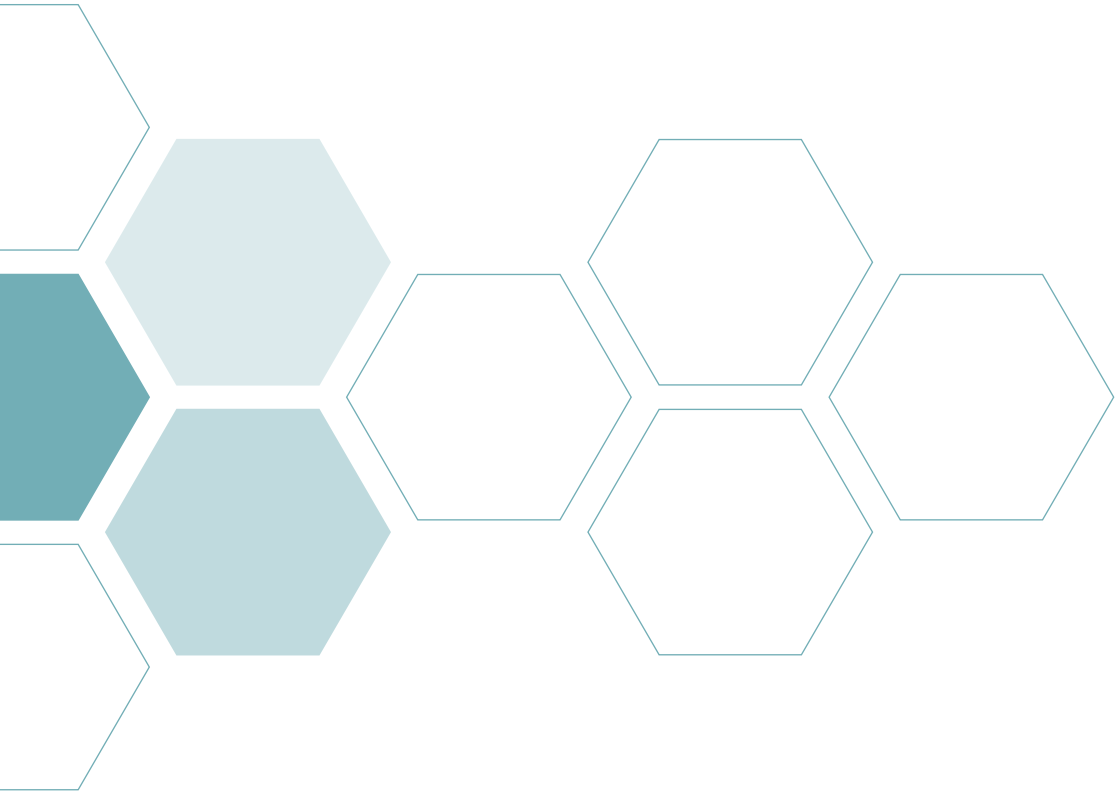
Vol. 22, No. 3, 2019

Educating Medical Directors of Employers, Health Plans and Provider Systems



FEATURED ARTICLES INCLUDE:

New Frontiers in the Management of Ovarian Cancer: Exploring the Role of PARP Inhibitors in the Evolving Treatment Paradigm

Optimizing Clinical and Economic Outcomes in the Management of Moderate to Severe Atopic Dermatitis: Taking a Closer Look at the Role of Biologic Therapies

Overcoming Challenges in the Clinical and Economic Management of Primary Immunodeficiency Diseases (PIDD): What Does Managed Care Need to Know About Immunoglobulin Replacement Therapy?

A Missed Opportunity to Recognize Narcolepsy Symptoms Can Have a Significant Impact on Pediatric Patients

Personality and Behavior

Anxiety, depression, introversion, feelings of inferiority, and sorrowfulness[1-3]

Academic

About 3.5 times higher likelihood of repeating a grade vs pediatric patients without narcolepsy[4]*

Economic

5 times higher medical costs vs pediatric patients without narcolepsy[5]†

Visit NarcolepsyLink.com/Pediatric to learn more about pediatric narcolepsy.

* Based on a health-related quality of life (HRQL) study assessed through a questionnaire completed by children and adolescents with narcolepsy (N=117) and control subjects (N=69). Academic performance was evaluated in the study.[4]

† Based on a retrospective, cross-sectional, case-control, claims-based analysis of health care utilization and costs, that included narcolepsy patients ≤18 years of age (N=1427) and control subjects (N=4281).[5]

References: 1. Nevsimalova S. Narcolepsy in childhood. *Sleep Med Rev.* 2009;13(2):169-180. **2.** Marcus C. Daytime sleepiness in children: when a quiet child is not necessarily a good thing. *Paediatr Respir Rev.* 2018;25:1-2. **3.** Blackwell JE, Alammar HA, Weighall AR, Kellar I, Nash HM. A systematic review of cognitive function and psychosocial well-being in school-age children with narcolepsy. *Sleep Med Rev.* 2017;34:82-93. **4.** Inocente CO, Gustin M-P, Lavault S, et al. Quality of life in children with narcolepsy. *CNS Neurosci Ther.* 2014;20(8):763-771. **5.** Reiss Reddy S, Broder MS, Tieu R, et al. Disease burden in pediatric narcolepsy: a claims-based analysis of health care utilization and costs and medical comorbidity. Poster presented at: SLEEP 2018, the 32nd Annual Meeting of the APSS; June 2-6, 2018; Baltimore, MD.

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NDS-0419d Rev1218

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A Peer-Reviewed Publication

Vol. 22, No. 3, 2019

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Editorial Review Board

SUNOSI™
(solriamfetol) IV
75, 150 mg tablets

NOW APPROVED

to treat excessive daytime sleepiness (EDS) in adult patients with narcolepsy or obstructive sleep apnea (OSA)

Images are not actual size.

INTRODUCING ONCE-DAILY SUNOSI

A NEW dual-acting daytime treatment for EDS indicated for adult patients with narcolepsy or OSA. SUNOSI is not a stimulant. SUNOSI 150 mg improved wakefulness through **9 HOURS** at week 12 in clinical trials.

Visit SUNOSIhcp.com or contact your Jazz Account Manager to learn more

INDICATIONS AND USAGE

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

Limitations of Use:

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Blood Pressure and Heart Rate Increases

SUNOSI increases systolic blood pressure, diastolic blood pressure, and heart rate in a dose-dependent fashion. Epidemiological data show that chronic elevations in blood pressure increase the risk of major adverse cardiovascular events (MACE), including stroke, heart attack, and cardiovascular death.

Please see following pages for additional Important Safety Information and Brief Summary of full Prescribing Information.

Jazz Pharmaceuticals

NOW APPROVED

SUNOSI 150 mg provided up to **9 HOURS** of wakefulness at week 12 in clinical trials

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Blood Pressure and Heart Rate Increases (cont'd)

The magnitude of the increase in absolute risk is dependent on the increase in blood pressure and the underlying risk of MACE in the population being treated. Many patients with narcolepsy and OSA have multiple risk factors for MACE, including hypertension, diabetes, hyperlipidemia, and high body mass index (BMI).

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

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

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

Psychiatric Symptoms

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

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

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

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

MOST COMMON ADVERSE REACTIONS

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

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

Reference: SUNOSI (solriamfetol) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. 2019.

SUNOSI™ (solriamfetol) IV
75, 150 mg tablets

Jazz Pharmaceuticals

SOL-0193a Rev0719

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

INDICATIONS AND USAGE

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

Limitations of Use

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

DOSAGE AND ADMINISTRATION

Important Considerations Prior to Initiating Treatment

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

General Administration Instructions

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Blood Pressure and Heart Rate Increases

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

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

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

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

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

Psychiatric Symptoms

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

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

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

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

ADVERSE REACTIONS

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

- Blood Pressure and Heart Rate Increases
- Psychiatric Symptoms

Clinical Trials Experience

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

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

Most Common Adverse Reactions

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

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

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

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

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

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

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

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

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

Other Adverse Reactions Observed During the Premarketing Evaluation of SUNOSI

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

Narcolepsy population:

Psychiatric disorders: agitation, bruxism, irritability

Respiratory, thoracic and mediastinal disorders: cough

Skin and subcutaneous tissue disorders: hyperhidrosis

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

Investigations: weight decreased

OSA population

Psychiatric disorders: bruxism, restlessness

Nervous system disorders: disturbances in attention, tremor

Respiratory, thoracic and mediastinal disorders: cough, dyspnea

Gastrointestinal disorders: constipation, vomiting

Investigations: weight decreased

Dose-Dependent Adverse Reactions

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

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

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

*In OSA only.

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

Adverse Reactions Resulting in Discontinuation of Treatment

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

Increases in Blood Pressure and Heart Rate

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

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

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

Monoamine Oxidase (MAO) Inhibitors

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

Drugs that Increase Blood Pressure and/or Heart Rate

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

Dopaminergic Drugs

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

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

Data

Animal Data

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

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

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

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

LACTATION

Risk Summary

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

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

Clinical Considerations

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

Pediatric Use

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

Geriatric Use

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

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

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

Renal Impairment

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance

SUNOSI contains solriamfetol, a Schedule IV controlled substance.

Abuse

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

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

Dependence

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

OVERDOSAGE

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

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

PATIENT COUNSELING INFORMATION

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

Potential for Abuse and Dependence

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

Primary OSA Therapy Use

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

Blood Pressure and Heart Rate Increases

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

Psychiatric Symptoms

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

Lactation

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

For more information, visit www.SUNOSI.com

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New Frontiers in Management of Ovarian Cancer: Exploring the Role of PARP Inhibitors in the Evolving Treatment Paradigm

Shannon N. Westin, MD, MPH

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

Summary

The identification of specific genetic mutations that can be targeted is transforming the treatment of ovarian cancer. One of these mutations is in BRCA, a mutation that leads to homologous recombination deficiency. PARP inhibitors are now available which improve survival in those with BRCA mutations and possibly other homologous recombination deficiency states.

Key Points

- PARP inhibitors are effective in women with ovarian cancer in the treatment and maintenance setting.
- The best outcomes with PARP inhibitors are observed in patients with BRCA mutation and some other DNA repair genes.
- These agents will likely be used much earlier in the disease process and in combination with other therapies in the future.

APPROXIMATELY 10 PERCENT OF OVARIAN cancers are hereditary. Women with germline mutations in the cancer susceptibility genes, BRCA1 or BRCA2, associated with Hereditary Breast and Ovarian Cancer syndrome, have up to an 85 percent lifetime risk of breast cancer and up to a 46 percent lifetime risk of ovarian, tubal, and peritoneal cancers.[1] In the general United States (U.S.) population, one in 300 women are positive for germline BRCA1 mutation and one in 800 for BRCA2 mutation.[2] This number is much higher in those of Ashkenazi heritage (1 in 40).[3] Screening for BRCA1/2 mutation on the basis of family history or young age at ovarian cancer diagnosis may miss a significant percentage of patients with BRCA1/2 mutation. Of women with BRCA-mutated ovarian cancer, 47 percent had no family history and 71 percent were over 50 years old.[4-6] The National Comprehensive Cancer Network (NCCN), the Society of Gynecologic Oncology and the American Society of Clinical Oncology guidelines suggest testing all patients with ovarian cancer for BRCA mutations.[1,7,8] It should be noted that there are other mutations which predispose women to develop ovarian cancer but these are not targeted by the poly ADP ribose polymerase (PARP) inhibitors, which are the focus of this article.

BRCA is involved in repairing breaks in double-stranded DNA though homologous recombination. Cells with BRCA mutations have nonfunctional homologous recombination but can repair DNA through base-excision repair — non-homologous end joining (NHEJ). Use of the NHEJ pathway alone results in genomic instability and increases the risk of developing breast, ovarian, prostate, and pancreatic cancer. PARP is involved in base-excision repair through NHEJ. PARP inhibitors prevent repair of breaks in single-stranded DNA and induce synthetic lethality in cells deficient in homologous recombination. Exhibit 1 shows how the PARP inhibitors work.

Exhibit 1: PARP Inhibitor Mechanism of Action

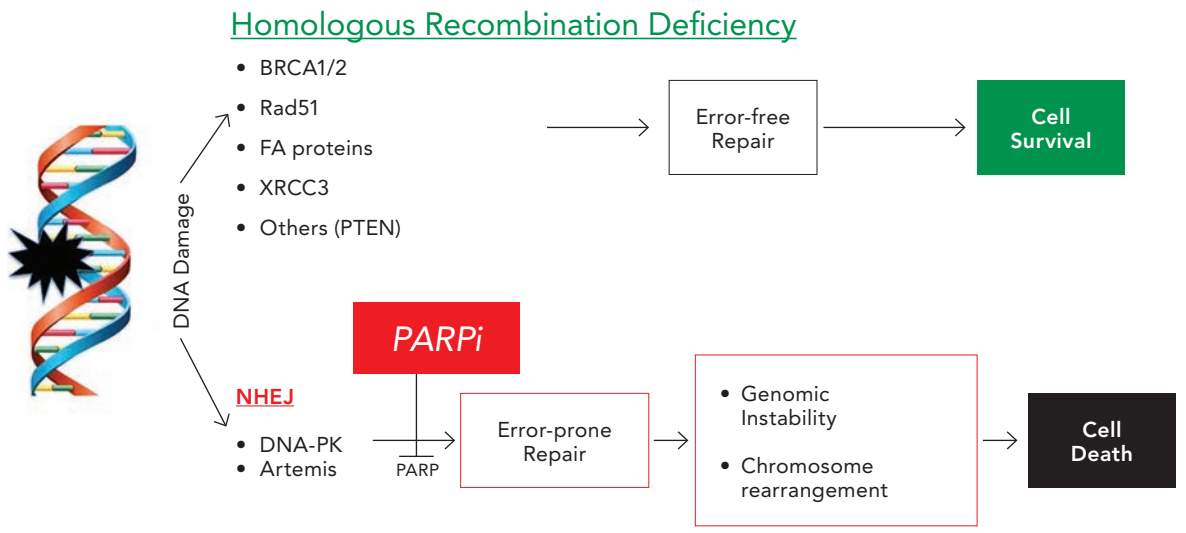
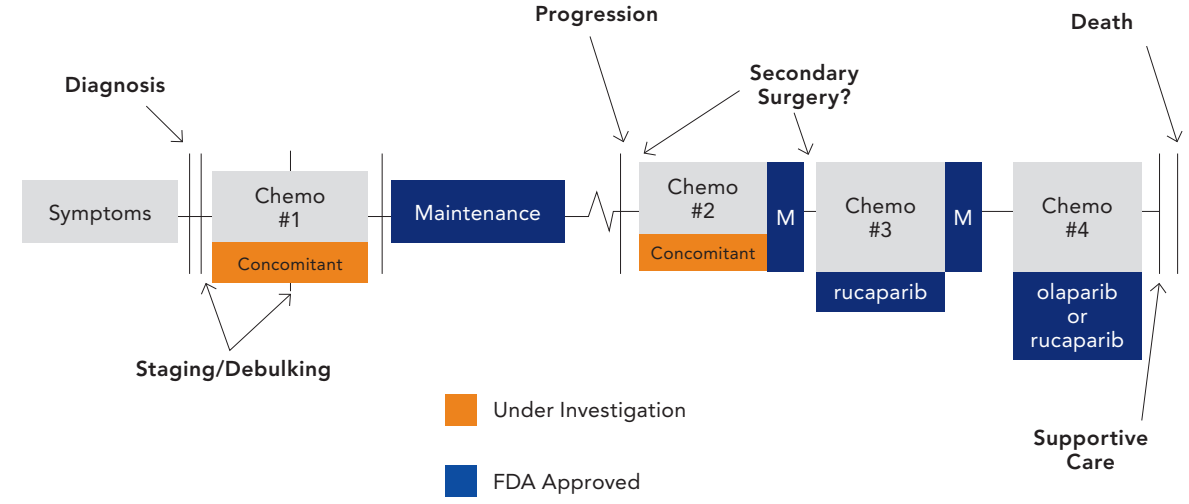


Exhibit 2: Treatment Paradigm for PARP Inhibitors in Ovarian Cancer



M = Maintenance with olaparib, rucaparib, or niraparib

The development and availability of PARP inhibitors has changed the treatment paradigm for ovarian cancer (Exhibit 2). The first PARP inhibitor for this disease was olaparib, which was FDA approved in 2014 for treatment of germline BRCA-mutated (gBRCAm) recurrent ovarian cancer. Rucaparib was approved in 2016 for gBRCAm and somatic BRCA-mutated (sBRCAm) recurrent ovarian cancer with greater than two lines of prior therapy. Niraparib and olaparib were approved in 2017 for maintenance of platinum-sensitive ovarian cancer after response to platinum-based therapy and rucaparib was approved in 2018. Exhibit 3 presents the FDA approved doses and indications for ovarian cancer. An additional PARP inhibitor, talazoparib, is currently only FDA approved for BRCA 1/2- re-

Exhibit 3: PARP Inhibitor FDA Approvals for Ovarian Cancer

Agent	Dose	Treatment Indication	Maintenance Indication
Olaparib (Lynparza®)	300 mg BID	gBRCAm ovarian cancer ≥ 3 prior therapies	Platinum-sensitive ovarian cancer after response to platinum-based therapy After first line platinum based chemotherapy in BRCAm/sBRCAm
Rucaparib (Rubraca®)	600 mg BID	gBRCAm/sBRCAm ovarian cancer ≥ 2 prior therapies	Platinum-sensitive ovarian cancer after response to platinum-based therapy
Niraparib (Zejula®)	300 mg QD	None	Platinum-sensitive ovarian cancer after response to platinum-based therapy

gBRCAm = germline breast cancer gene mutation
sBRCA = somatic breast cancer gene

Exhibit 4: Platinum-Sensitive Relapse RCTs Maintenance After Chemotherapy[9-13]

Status	Study 19	SOLO-2	NOVA	ARIEL3
Population	HGSC	gBRCA^{mut}	I: gBRCA^{mut} II: Non-gBRCA HGSC	HGSC or endometrioid
Design	Phase II	Phase III	Phase III	Phase III
Regimen	Olaparib vs placebo	Olaparib vs placebo	Niraparib vs placebo	Rucaparib vs placebo
PFS (months)	8.4 vs 4.8	19.1 vs 5.5	21.0 vs 5.5	16.5 vs 5.4 (BRCAmut)
N (randomization)	265 (2:1)	295 (2:1)	469 (2:1)	540 (2:1)

HGSC = high-grade serous carcinoma
PFS = progression-free survival

lated breast cancer. The use of PARP inhibitors in ovarian cancer will continue moving earlier into the disease process as more studies are done.

Exhibit 4 shows the efficacy data for PARP inhibitors as maintenance after chemotherapy to prevent relapse in platinum-sensitive disease BRCA-mutated disease.[9-13] The NCCN guidelines recommend olaparib as first-line maintenance therapy after primary treatment for patients with BRCA1/2 mutations in complete clinical remission or partial remission.[14] The recommendation is Category 1 for germline mutations and Category 2B for somatic mutations. This recommendation comes from a trial of newly diagnosed Stage III – IV disease in which olaparib given post-surgery and first-line platinum-based chemotherapy significantly increased PFS. Sixty percent of those in the olaparib group were progression free at three years compared to 26.9 percent in the placebo group.[15] Any of the PARP inhibitors approved for maintenance are an option

after response to the second or later course of platinum-based chemotherapy.[14]

Bevacizumab is also recommended for maintenance therapy post-remission for patients with partial or complete responses who received it in primary treatment, or for patients with stable disease.[14] Clinicians have to make a decision whether to offer bevacizumab or a PARP inhibitor for maintenance in those patients who received bevacizumab in primary treatment.

Olaparib and rucaparib are considered recommended treatments for recurrent ovarian cancer that is platinum-sensitive, instead of chemotherapy or bevacizumab. In the trials of these two agents, patients had received a median of two or three prior lines of platinum-based chemotherapy. The overall response rates were 33 to 40 percent.[16-18] In the rucaparib trial, the progression-free survival was 12.8 months in BRCA mutation positive patients.[16]

Efficacy of the PARP inhibitors appears consistent among the agents with no major differences demonstrated so far. The choice of agent will depend on indication, dosing schedule (twice a day versus once daily), adverse effects, concomitant diseases, and cost based on contracting.

Beyond BRCA there are numerous other mechanisms of homologous recombination deficiency (HRD). Over 50 percent of tumors in one trial were found to be deficient or possibly deficient.[19] Research is ongoing to identify which HRD mutations are responsive to PARP inhibition. At least some are because responses have been seen in BRCA wild-type patients. For example, in a rucaparib trial the overall response rate was 69 percent in those with BRCA mutation, 30 percent in those with BRCA-like signature (loss of heterozygosity high), and 13 percent in those who were BRCA wild-type.[16] The median progression-free survival was 12.8, 7.2, and 5.0 months, respectively. A HRD score, a measure of genome instability, has been developed in an attempt to find a biomarker of PARP inhibitor response beyond just BRCA mutations. The HRD score is the sum of three independent biomarkers: telomeric-allelic imbalance (TAI), large-scale state transitions (LST), and loss of heterozygosity (LOH).[20-22] The HRD score is calculated from single-nucleotide polymorphism-derived whole genome profiling.

Even though PARP inhibitors are "just a pill," there are adverse effects which can be significant. Anemia, thrombocytopenia, and neutropenia are the most common hematologic adverse effects. Nausea, fatigue, vomiting, and diarrhea are the most common non-hematologic adverse effects. Thrombocytopenia is typically transient and managed by dose modification and dose holding. Patients who are smaller will typically need lower doses to prevent significant hematologic toxicity. [23] Unique to rucaparib is a higher rate of increased creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Hypertension has been reported with niraparib. Not common, but of concern, is treatment-induced acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), which has been reported in 0.5 percent with rucaparib, 1.4 percent with niraparib, and 0.8 percent with olaparib.[24-26]

Monitoring for adverse effects should be done weekly for the first few months and then at least once a month for the first year of therapy. Clinicians can consider starting weekly home nursing visits, if necessary. Dose reductions and therapy delays can be used liberally, especially for Grade 3 or 4 toxicity. Because of the potential for hematologic toxicity, patients should have recovered from all prior therapy-related hematologic toxicity before starting a PARP inhibitor. If hematologic toxicities do not resolve within four weeks of discontinuing the PARP inhibitor, a workup for AML/MDS should be done. Timing dosing around meals and aggressive early use of antiemetics can help prevent and manage nausea. Laxatives and antidiarrheals may also be needed to manage other gastrointestinal issues. It is important to manage expectations of patients and caregivers to alleviate key symptoms in order that therapy can continue uninterrupted.

Conclusion

Data support important clinical efficacy of PARP inhibitors in women with ovarian cancer in the treatment and maintenance setting. Consistent with the mechanism of action of these agents, the best outcomes are observed in patients with BRCA mutation and some other DNA repair genes. Biomarker scores of HRD are being developed to better identify patients who will respond to these agents. A number of studies targeting combinations are underway using PARP inhibitors earlier in the course of treatment.

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Building a Better Understanding in Asthma Management: Best Practices for Treatment and Control

Michael E. Wechsler, MD, MMSc

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

Summary

Several very effective therapies have been approved for treating severe asthma. The type of asthma a given patient suffers is key to selecting which of the new therapies should be used. Because the new therapies are expensive, the use of them should be selected carefully.

Key Points

- Patients with allergic asthma, which is not well controlled with high-dose inhaled corticosteroids and an additional controller medication, can be considered for treatment with omalizumab.
- Patients with severe eosinophilic asthma that is not controlled with inhaled corticosteroid and long-acting beta agonists may benefit from an interleukin-5 (IL-5) inhibitor (mepolizumab, reslizumab, or benralizumab).
- Dupilumab should be considered for eosinophilic or type 2 moderate to severe asthma and steroid-dependent asthma.

ASTHMA IS A HETEROGENEOUS DISEASE, characterized by chronic airway inflammation and a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, cough that varies over time and in intensity, and variable airflow limitation.[1] Inflammation, bronchoconstriction, and excess mucus play a major role in producing the symptoms of asthma (Exhibit 1). The narrowed airway of asthma makes breathing difficult. Treatments of asthma target the bronchoconstriction and inflammation.

Asthma is a highly prevalent disease, affecting 26 million people in the United States (U.S.), including six million children.[2] The rate is higher in women and in African Americans. Asthma causes a significant personal and financial burden. There are approximately 11 million physician office visits with asthma as the primary diagnosis, 1.7 million emergency room visits, and 3,500 deaths annually as a result of asthma.[3] The overall cost of asthma is estimated as $81.9 billion in the U.S.[4] Those with severe asthma are the most costly (Exhibit 2).[5] Better management and utilization strategies for the newer novel treatments are needed to help manage those with severe asthma to mitigate the burden of disease.

Asthma is classified by persistence, severity, and type. Patients can have intermittent or persistent asthma. Persistent asthma is classified as mild, moderate, or severe.[6] Severe asthma is asthma, which despite patient adherence, requires high-dose inhaled corticosteroids (ICS), plus long-acting beta agonist LABAs and/or additional controller medication, or requires oral corticosteroids (OCSs) to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy.[7] Severe asthma is estimated to affect 5 to 10 percent of the total asthma population.[8]

Severe asthma can be broken down into two groups: difficult-to-control disease and true severe asthma. Difficult-to-control asthma is a lack of asthma control due to factors other than asthma itself

Exhibit 1: The Asthmatic Airway Compared to a Normal Airway

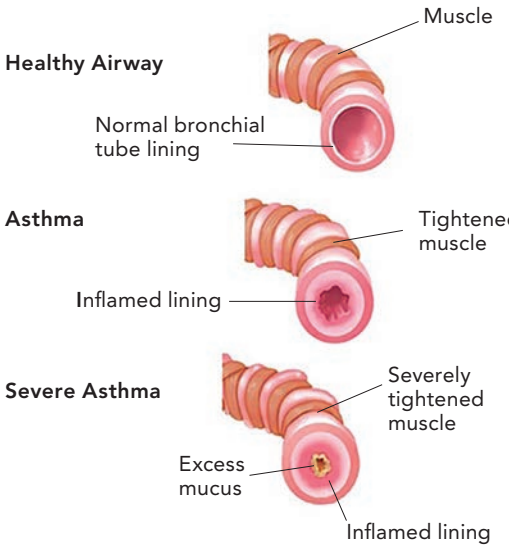
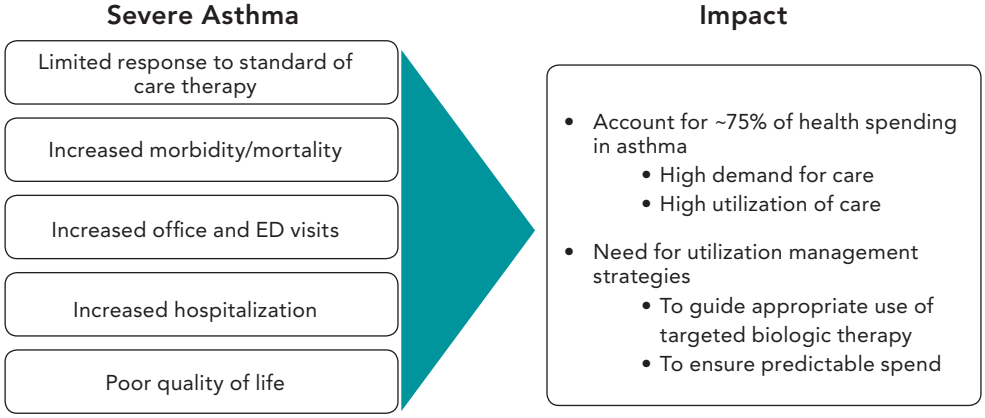


Exhibit 2: Managed Care Perspective on the Burden of Severe Asthma

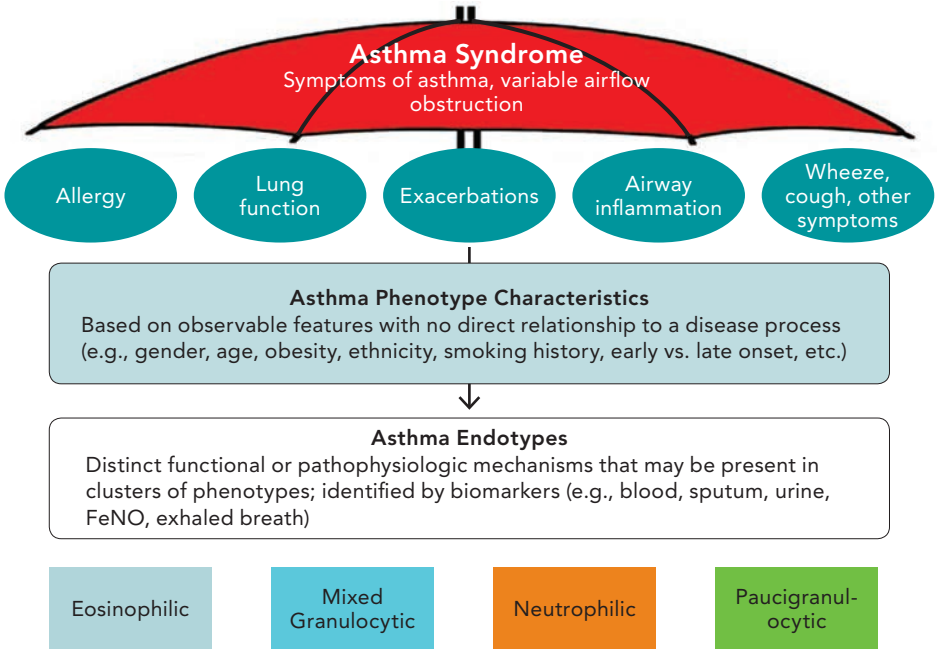


(e.g., nonadherence, incorrect inhalation technique, comorbidities), and it accounts for 90 percent of those who are labeled as having severe asthma. True refractory or severe asthma is poor asthma control or two or more exacerbations per year despite high-intensity treatment, verified adherence, and causes of difficult asthma addressed or excluded.

Asthma is not just one disease (Exhibit 3).[9,10] Different asthma phenotypes and endotypes respond to different therapies. Asthma phenotypes include trigger-induced and clinical presentation types. Allergic, non-allergic, infection, exercise-induced, and aspirin-exacerbated respiratory disease (AERD) are all trigger-induced phenotypes. Pre-asthma wheezing in infants, episodic (viral) wheeze, multi-trigger wheezing, exacerbation-prone asthma, and asthma associated with apparent irreversible airflow limitation are clinical presentation types. The two endotypes are type 2 high (eosinophilic asthma) and type 2 low. The future of clinical care is to transition from phenotype and endotype classifications to genotype.

Those with type 2 high have IL-4, IL-13, and IL-5- mediated disease that is set off by antigens and/or allergens. Biomarkers for this endotype are eosinophilia, elevated IgE, and elevated FeNO. This endotype usually has an earlier in life onset compared with type 2 low and allergic sensitization. Co-

Exhibit 3: Asthma is Not Just One Disease[9,10]



morbidities include chronic sinusitis with or without nasal polyps and atopic dermatitis. Type 2 inflammation is prevalent in patients with uncontrolled persistent asthma, and these patients have the highest disease burden.

Type 2 low disease is mediated by IL-6, IL-17, and TNF. Paucigranulocytic and neutrophilia are biomarkers for Th2 low. Neutrophilic disease is set off by irritants, pollutants, microbes, and viruses. Paucigranulocytic asthma has normal levels of both eosinophils and neutrophils. This endotype is typically later in life onset with obesity, infections, and smoking as comorbidities. Paucigranulocytic disease may not warrant anti-inflammatory therapy. These patients, whose symptoms may be driven largely by airway hyper-responsiveness, may benefit from smooth muscle-directed therapies, such as bronchial thermoplasty or mast-cell directed therapies.

Due to the fast pace of innovation, asthma treatment guidelines often do not reflect the most recently introduced treatment options. The National Asthma Education and Prevention Program guidelines were last updated in 2007 and the International European Respiratory Society (ERS) and the American Thoracic Society (ATS) Guidelines on Severe Asthma in 2014.[6,7] The Global Initiative for Asthma (GINA) guidelines were updated in 2018 and include the use of endotype to select therapy and all the new therapies.

Exhibit 4 presents some general principles of asthma management.[1,6] In addition to these general principles, it is important that inhaler technique and adherence be checked at each health care visit. Concomitant diseases, which can complicate asthma management, have to be managed (sinusitis, obstructive sleep apnea, vocal cord dysfunction, and acid and nonacid reflux) in order to achieve good asthma control.

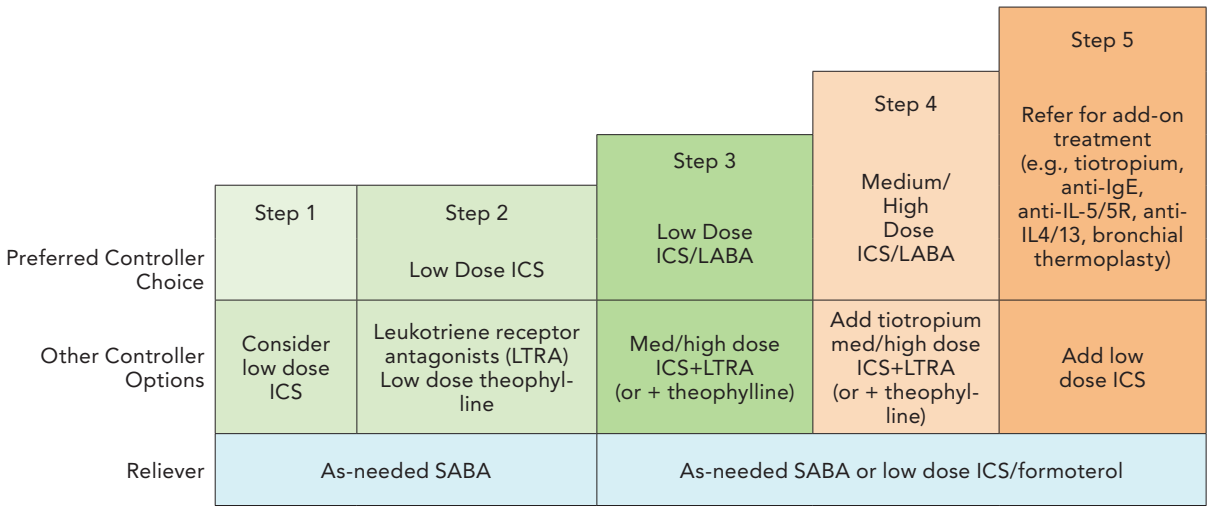
The benchmarks of good asthma control are no coughing or wheezing, no shortness of breath or rapid breathing, no waking up at night (due to asthma symptoms), normal physical activities, no school absences or missed work due to asthma, and no missed time from work for parent or caregiver. To achieve good asthma control, clinicians can use the management guidelines to guide therapy and monitor both subjective and objective information such as spirometry, Asthma Control Test or other symptom questionnaires, and laboratory values.

The stepped-care approach from the 2018 GINA guidelines are shown in Exhibit 5.[1] Therapy is stepped up if the patient is not well-controlled and can be stepped down if the disease is controlled for a period of time. If symptoms remain uncontrolled or exacerbations persist despite Step 4 treatment, clinicians need to check the patient's inhaler technique and adherence before referring. If asthma is being managed by a primary care provider, individuals

Exhibit 4: General Principles of Asthma Management[1,6]

- Determine that the disease is actually asthma
- Assess asthma severity and degree of control
  - **Severity:** the intrinsic intensity of the disease process
  - **Control:** the degree to which the manifestations of asthma are minimized by therapy
- Assess impairment and risk
  - **Impairment:** the frequency and intensity of symptoms and functional limitations
  - **Risk:** the likelihood of asthma exacerbations, progressive decline in lung function or adverse effects from medication
- Employ a control-based management approach to treatment
  - Continuously review the response to treatment and adjust as needed to achieve/maintain control
- Consider patient characteristics, phenotype, endotype, preferences, and practical issues (e.g., adherence, cost, etc.) when selecting therapy and evaluating response
- Establish a partnership between the person with asthma and health care providers

Exhibit 5: 2018 GINA-Recommended Asthma Pharmacotherapy[1]



ICS = inhaled corticosteroid
LABA = long acting beta agonist
SABA = short acting beta agonist
IL = interleukin

with severe asthma should be referred to an asthma specialist for management. Treatment of severe asthma requires an extensive workup to determine endotype. Step 5 add-on options are numerous. Tiotropium is an option for patients 12 years of age and older with a history of exacerbations. The novel biologic agents are also options for severe asthma with allergic or eosinophilic asthma (Exhibit 6). Other add-on treatment options at Step 5 include sputum-guided treatment, low-dose oral corticosteroids (≤7.5mg/day prednisone equivalent), and bronchial thermoplasty. Sputum-guided therapy is available in specialized centers and reduces exacerbations and/or corticosteroid dose. Oral steroids may benefit some patients, but they cause significant systemic side effects and thus should be avoided.

About 50 percent of severe asthma cases are mediated by eosinophilic cytokines. IL-5 is one of the primary cytokines which regulates proliferation, maturation, migration and effector functions of eosinophils. IL-5 mRNA is increased in patients with asthma, correlates with asthma severity, and is in-

Exhibit 6: Novel Therapies for Severe Asthma

Drug/ Mechanism of Action	Endotype	Dosing	Frequency	Route	Exacerbation Reduction Rate (vs. Placebo)	Increased FEV_1 (vs. Placebo)
Omalizumab (Xolair®) Anti IgE	Allergic asthma	125mg – 375mg (based on weight/ IgE level)	Q2W or Q4W (depending on weight/ IgE level)	Sub-Q	33% to 75%	Not significant
Reslizumab (Cinqair®) Anti IL5	Eosinophilic asthma	3.0mg/kg	Q4W	IV	50% to 59%	110 - 126ml
Mepolizumab (Nucala®) Anti IL5	Eosinophilic asthma	100mg	Q4W	Sub-Q	53%	98ml
Benralizumab (Fasenra®) Anti IL5 Receptor	Eosinophilic asthma	30mg	Q8W (first 3 doses every 4 weeks)	Sub-Q	36% to 55% (Q4W frequency) 28% to 70% (Q8W frequency)	0 - 125ml
Dupilumab (Dupixent®) Anti IL4 Receptor	Eosinophilic asthma	200 - 300mg	Q2W	Sub-Q	59.9% to 80.7%	390 - 430ml

Q = every
W = week
Sub-Q = subcutaneous
IV = intravenous

ducible by allergen exposure. Anti-IL-5 agents (mepolizumab, reslizumab, benralizumab) reduce exacerbations, improve lung function, and reduce need for steroids compared to placebo.[11-17]

Dupilumab, which was first approved for atopic dermatitis, is an anti-IL-4/IL-13 agent which has a broader effect than the anti-IL-5 agents, so it can target both eosinophilic asthma and non-type 2 inflammation (~65% of severe asthma population). It was FDA approved for moderate to severe eosinophilic asthma or steroid-dependent asthma; the anti-IL-5 agents are only approved for severe asthma. This agent significantly lowered rates of exacerbations and improved lung function.[18,19] Patients in the trial were taken off of ICS and still had a significant reduction in exacerbations.

Omalizumab blocks IgE binding to mast cells which prevents release or production of numerous mediators of asthma symptoms, including histamine, TNF, proteases, heparin, prostaglandins, leukotrienes, IL-4, and IL-13. This agent reduces exacerbations and symptoms.[20] It is FDA approved for moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids.

There are numerous questions that need to be answered about the use of novel therapies. Because there are no comparison trials, it is unknown if any of the anti-IL-5 agents are more effective, or if the anti-IL-4/13 agent is more effective than anti-IL-5. Studies are needed to help clinicians and payers decide between the different biologics based on existing biomarkers. A combination of different mechanism of action biologics will also need to be studied. The best therapies for non-type 2 severe asthma are unknown, but need to be determined.

The increasing number of biologic agents for severe asthma requires careful consideration of the asthma pharmacy benefit. The overall spend on traditional asthma therapies covered in the pharmacy benefit is decreasing. The reductions are mainly driven by increased competition and rebate strategies. With the growing number of biologics on the market and more in the pipeline, asthma treatment is becoming increasingly targeted and patient specific. Consequently, asthma spending trends are beginning to increase through the medical benefit.[21]

There are also numerous other agents under investigation for severe asthma targeting other biomarkers. These include fevipiprant, an oral prostaglandin DP2 receptor (CRTh2) antagonist, tezepelumab, a thymic stromal lymphopoietin (TSLP) antagonist,

and antagonists against IL-25, IL-33, and IL-17.

A novel, non-drug approach to asthma is bronchial thermoplasty, which aims to treat asthma by disrupting airway smooth muscle. All visible and reachable airways distal to mainstem bronchi are treated with a series of contiguous activations. In a published trial of the procedure, a 44 percent reduction in severe exacerbations requiring systemic corticosteroids compared to a sham treatment was maintained out to at least five years.[22] This is a good option for patients with severe non-type 2 asthma.

Conclusion

Response to asthma therapies is variable and based on patient and disease factors. Patients with severe asthma require additional evaluation and referral to an asthma specialist for endotyping and consideration of add-on therapy. Biologics should be considered for those with moderate to severe allergic and eosinophilic asthma.

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Optimizing Clinical and Economic Outcomes in the Management of Moderate to Severe Atopic Dermatitis: Taking a Closer Look at the Role of Biologic Therapies

Mark G. Lebwohl, MD

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

Summary

Atopic dermatitis can majorly impact a patient's life, depending on the severity of the disease and the itching it causes. Numerous treatments including topical corticosteroids, systemic corticosteroids, topical calcineurin inhibitors, topical PDE4-inhibitors, systemic immunosuppressants, phototherapy, and biologics are available. The biologics are making the greatest difference in clearing the skin and improving quality of life for those with moderate to severe disease.

Key Points

- Atopic dermatitis causes major impact on quality of life for patients and caregivers.
- Crisaborole is an effective agent for mild to moderate atopic dermatitis, causing fewer adverse effects than corticosteroids or calcineurin inhibitors.
- Dupilumab is now available for moderate to severe atopic dermatitis.

ATOPIC DERMATITIS (AD) IS A COMMON chronic inflammatory skin disease, often starting in childhood. It manifests as eczematous rashes, itch, bacterial colonization and secondary infections. The course of AD can be intermittent or persistent, and the severity ranges from mild to severe. The prevalence of atopic dermatitis varies around the world, and it has been reported to occur in 2.6 to 10.3 percent of the population, depending on the country.[1] The rate is higher in children, those living in metropolitan areas, and among African Americans.

There is an association of childhood AD and other atopic diseases. Those with AD are more likely to also have or develop asthma, respiratory allergies, rhinitis, and food allergies.[2] AD is typically the first atopic disease, followed closely by food allergies; asthma and rhinitis tend to develop later in childhood. This has been called the Atopic March. There is a theory that if AD could be prevented or minimized then the rest of the March could be prevented; however, this has not yet been proven.

AD presents as dry and scaly patches on the scalp, forehead, and face (particularly the cheeks), and on the flexor surfaces of the arms, feet, legs, and neck; however, lesions can appear anywhere on the body. Children tend to have a different pattern of skin lesions than adults. The AD lesions are typically intensely pruritic, excoriated, and have exudation from microscopic skin blistering. Because of the exudation and scratching, the skin of those with AD is almost always colonized with staph aureus. One set of criteria for AD diagnosis is shown in Exhibit 1.[3] The three main features of AD are itching, it starts early in life, and it is chronic or recurs chronically.

AD is not just a skin disease. It has several significant non-allergic comorbidities, including depression, autism, attention deficit hyperactivity disorder, and infection.[4-6] The prevalence and severity of comorbidities is related to the underlying disease severity.[7] Emerging comorbidities include cardio-

Exhibit 1: Atopic Dermatitis (AD) Criteria[3]

Major criteria (must have three or more of)	Pruritis Early age of onset Typical morphology and distribution Flexural lichenification and linearity in adults Facial and extensor involvement during infancy and childhood Chronic or chronically relapsing dermatitis Personal or family history of atopy (asthma, allergic rhino conjuctivitis, AD)
Minor or less specific criteria (should have three or more of)	Xerosis Ichthyosis, palmar hyperlinearity, keratosis pilaris Immediate (type 1) skin test reactivity Raised serum IgE Early age of onset Susceptibility to cutaneous infections (especially *Staphylococcus aureus* and herpes simplex) or impaired cell-mediated immunity Tendency toward non-specific hand or foot dermatitis Nipple eczema Cheilitis Recurrent conjunctivitis Dennie - morgan infraorbital fold Keratoconus Anterior subcapsular cataracts Orbital darkening Facial pallor or facial erythema Pityriasis alba Anterior neck folds Itch when sweating Intolerance to wool and lipid solvents Perifollicular accentuation Food intolerance Course influenced by environmental or emotional factors White dermatographism or delayed blanch

vascular disease, obesity, osteoporosis and bone fractures , increased rate of accidents, vitiligo, alopecia areata, visual problems, and dental issues.[7-11] Some of these emerging comorbidities are likely related to extensive use of topical and systemic corticosteroids.

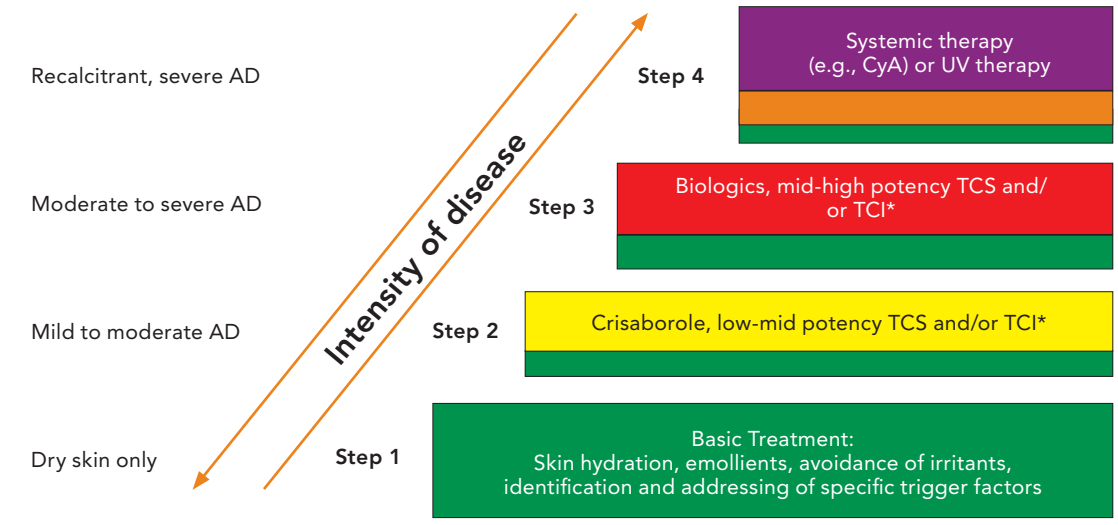
Sleep disturbance because of itching is common and is a major issue for patients and parents of children with AD. Sleep disturbances are seen in approximately 60 percent of children with AD.[12] This increases to 83 percent during disease exacerbations.[12] Even in clinical remission, children with AD demonstrate more sleep disturbance than healthy children. [12] Parental sleep disturbance also occurs.[13]

The pathophysiology of AD, which results in a dysfunction skin barrier, is multifactorial, where multiple genes and environmental factors contribute to immune dysregulation. Dysregulation of T helper cell one and two (TH1, TH2) mediated cytokines occurs. Th2 factors that play a role in AD include interleukin four (IL-4), IL-13, and IL-31. IL-4 and IL-13 are elevated in acute and chronic skin lesions of AD.

The management of AD varies, depending on the severity. Exhibit 2 shows a stepwise plan based on severity, which has been updated to include the newly approved agents.[14] Keeping the skin moisturized is vital to AD management and is important at all severity levels. Bathing is controversial for helping with skin moisturization. In one trial, bathing increased skin hydration 91 percent, bathing paired with immediate or within 30 minutes moisturizer increased it 141 percent, and moisturizer alone was most effective with a 206 percent increase in hydration.[15] Most clinicians recommend quick showers with moderate temperature water and multiple daily applications of moisturizers even when the disease is not active.

Topical corticosteroids (TCS) are the most commonly used treatment to manage AD. Although effective, they can cause significant adverse effects, including irreversible striae and thinning of the skin. If used appropriately, these agents can be safe. If used on the face or intertriginous areas (armpits, under breast, medial aspect of thigh), there is a much higher risk of adverse effects. TCS are also not appropriate for use in patients who have extensive lesions because of the possibility of systemic absorption. Use of eyelid TCS and systemic corticosteroids can cause glaucoma and cataracts. Systemic corticoste-

Exhibit 2: Stepwise Management of AD[14]



*Over age of two years

CyA = cyclosporine A
TCI = topical calcineurin inhibitors
TCS = topical corticosteroid

roids have been used for extensive disease, but they cause the most adverse effects, including suppression of adrenal gland function, osteoporosis, and type 2 diabetes. Many insurers require use of TCS before moving on to other agents; however, this may not be the best approach in a chronic skin disease that requires long-term treatment.

Crisaborole is a newer topical option. This is a boron-based, nonsteroidal, anti-inflammatory phosphodiesterase four (PDE4) inhibitor. It is effective for mild to moderate AD and is much safer than topical corticosteroids and topical calcineurin inhibitors. It is even safe for use on the eyelids because it does not cause increased intraocular pressure.

Topical calcineurin inhibitors, tacrolimus and pimecrolimus, are effective agents for mild to severe AD.[16] Up to two years of use in infants has been shown to be safe and well tolerated.[17] As with crisaborole, they appear to be a safe option for use on the eyelids to avoid increases in intraocular pressure that can occur with TCS.[18]

Nonspecific systemic immunosuppression has also been used to treat severe AD. Cyclosporine, methotrexate, and mycophenolate mofetil have all been used for AD but are not FDA approved for this indication and cause significant adverse effects. Cyclosporine is the most effective of these for severe AD and works relatively quickly.[19] One year of cyclosporine is the maximum duration of therapy recommended over one's lifetime for AD, and monthly laboratory monitoring is required. It can cause nephrotoxicity, hypertension, hypomagnesemia, hyperkalemia, hyperlipidemia, hypertrichosis, and lymphoproliferative disease. It also interacts with numerous other medications. Prior to the approval of biologics, it was the most commonly used immunosuppression.

Dupilumab is the most recently approved therapy for AD. It is a monoclonal antibody that blocks the IL-4/IL-13 receptor/ligand system (Exhibit 3). It has been studied in moderate to severe AD in combination with TCS and as monotherapy. In a difficult to treat population (resistant to cyclosporine, >50 percent body surface area affected), the combination significantly improved efficacy measures compared with TCS alone.[20] One hundred percent of patients had at least 50 percent clearing of their skin (EASI50). Patients on dupilumab in combination with TCS used approximately 50 percent less TCS during the treatment period compared with patients on placebo plus TCS (48.7g vs 99.4g). In the three major trials (combination or monotherapy), more subjects receiving dupilumab obtained EASI75, EASI 50, or investigator rating of 1 or 0 than placebo or TCS groups at 16 weeks.[20-22] Pruritis is significantly decreased by dupilumab and quality of life is improved significantly. The disease response and

Exhibit 3: Dupilumab Mechanism of Action

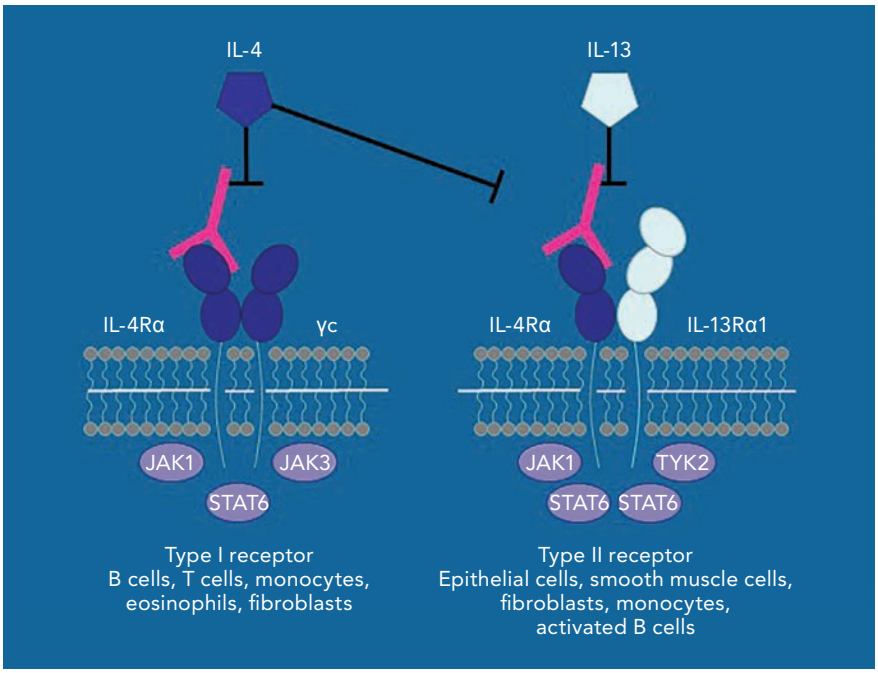
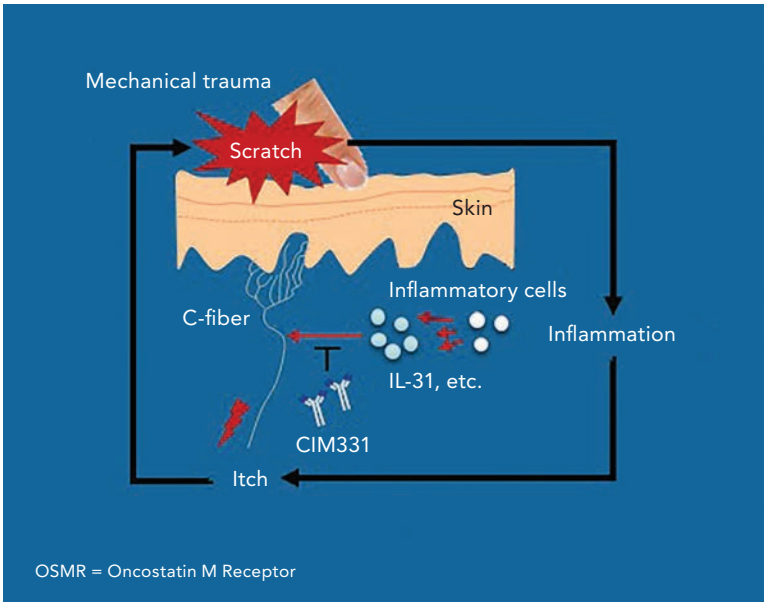


Exhibit 4: Why Interleukin-31 is Important to AD?



effect on pruritus appears to plateau at week 24 of therapy and be sustained to week 52.[20] Patients were less likely to discontinue therapy in the dupilumab with TCS groups compared to placebo with TCS group (15% in both dupilumab groups compared to 33% placebo).[20] The most common adverse effects with dupilumab are injection site reactions and conjunctivitis.

Phototherapy, with or without psoralen, can be an effective treatment option for moderate to severe

AD, but it is not as effective as dupilumab. Rates of skin clearing with phototherapy are high (>75%) but only occur in a small percentage of patients.[23] Adverse effects of phototherapy include squamous cell carcinomas. One benefit of phototherapy is the killing of staph aureus on the skin. Because it requires three office visits weekly and three to six months of use to see benefit, phototherapy is not commonly used now that dupilumab is available. Phototherapy works much better for psoriasis.

Treatment of staph aureus colonization can also decrease disease severity in some patients.[24] Bathing twice a week for 5 to 10 minutes in half a tub of bathwater with a half-cup of bleach added is an appropriate option for those with obvious topical infections.

Anti-IL-13, anti-thymic stromal lymphopoietin (TSLP), and anti-IL-31 monoclonal antibodies are under investigation for AD. Tralokinumab and lebrikizumab are anti-IL-13 agents. Tezepelumab is an anti-TSLP agent. IL-31 is a pruritogenic cytokine and the itch-scratch-cycle is an exacerbating factor of AD (Exhibit 4). Nemolizumab is an anti-IL-31 antibody expected to improve pruritus and ameliorate dermatitis by breaking itch-scratch-cycle. It improves pruritis scores, improves dermatitis, reduces weekly corticosteroid use, and improves hours asleep.[25]

Conclusion

AD is not just a skin disease. It has a major impact on quality of life and because it is an inflammatory disease it leads to significant comorbidities. The management of severe AD is being transformed with the availability of dupilumab, which targets the pathology of the disease. Additional biologics are on the horizon and will continue to transform care.

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Novel Treatment Advances and Approaches in the Management of Advanced Breast Cancer: Expert Strategies for Individualized Treatment

Adam M. Brufsky, MD, PhD

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

Summary

Triple-negative breast cancer is a difficult to treat cancer, particularly once it becomes metastatic. The only therapy choice has been chemotherapy. However, there is now an effective targeted therapy available for about 25 percent of those with metastatic triple negative breast cancer who have a specific genetic mutation.

Key Points

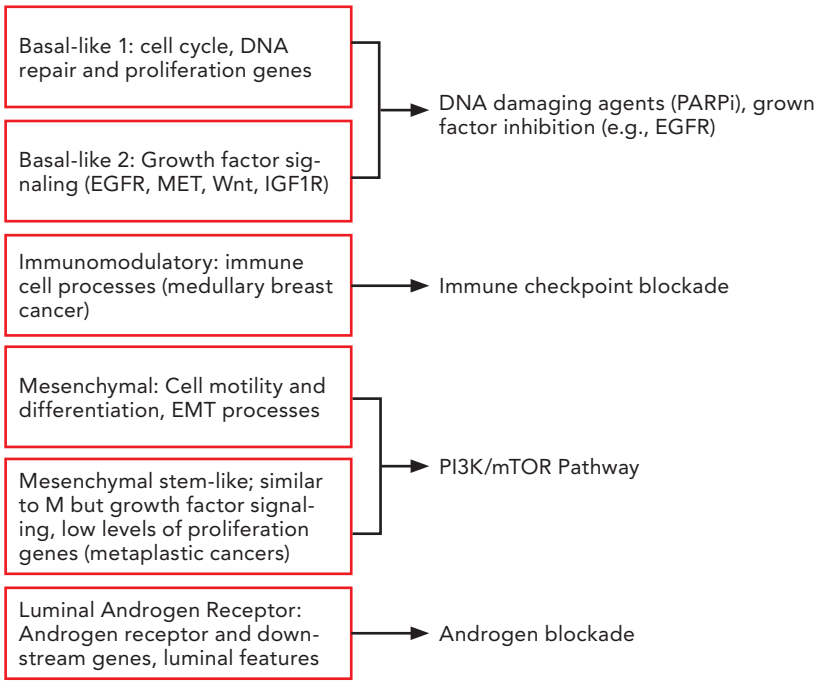
- Fifteen to 20 percent of metastatic breast cancer cases are triple-negative breast cancer (TNBC).
- Traditional treatment of metastatic TNBC has been chemotherapy.
- About 24 percent of TNBC tumors have BRCA 1 or 2 mutations, which makes the tumor susceptible to PARP inhibition.
- The approval of two PARP inhibitors to treat metastatic breast cancer with these mutations is revolutionizing treatment and is the first targeted therapy for TNBC.

IN METASTATIC BREAST CANCER, APPROXimately 50 percent of the cases will be hormone-receptor positive, with a five- to six-year average survival with anti-hormonal therapy. The 20 to 25 percent with HER2-positive metastatic disease have a similar average survival with targeted therapy. Fifteen to 20 percent of metastatic cases are triple-negative breast cancer (TNBC); this has a diagnosis of exclusion because the hormone receptors and HER2 are negative. Unfortunately, the survival with TNBC is significantly less than with other types of metastatic breast cancer.

It is now known that TNBC is not just one disease. There are at least six subtypes of TNBC that have been identified for which there are potential therapeutic approaches (Exhibit 1).[1] The treatment of TNBC is changing rapidly and will continue to evolve over the next few years as the subtypes are better characterized. The use of poly ADP-ribose polymerase inhibitors (PARPi) in the treatment of TNBC which is positive for BRCA 1 and 2 mutations is the focus of this article.

When all patients with metastatic TNBC were treated the same, first-line systemic therapy was chemotherapy with paclitaxel, platinum, gemcitabine/carboplatin, or taxane/carboplatin. The median progression-free survival (PFS) with first-line chemotherapy is 4.6 months, and the median overall survival (OS) is 12 to 18 months. The second-line option at progression is a therapy the patient did not receive first-line. Second-line median PFS is 2.9 months and median OS is eight months. Third and fourth-line therapies are eribulin and ixabepilone with or without capecitabine, respectively.

Exhibit 1: Potential Therapeutic Approaches in TNBC[1]



Because widespread testing to determine the TNBC subtype is not yet available, clinicians have to use immunohistochemistry and other characteristics of the tumor to fit it into a subtype to select treatment. A marker of the basal-like1 subtype is DNA repair deficiency, which is prevalent in various solid tumor types. About 15 percent of TNBC cases have DNA repair deficiency.[2,3]

External and internal insults are always causing cellular DNA damage. External insults include smoking, pollution, radiation, and chemotherapy. Internal insults include replication errors and spontaneous mutations. This DNA damage is repaired via multiple pathways, including base excision repair (BER), homologous recombination (HR), and nonhomologous end joining (NHEJ).[4] When there is an imbalance between damage and repair which leads to an accumulation of mutations, cancer can occur.

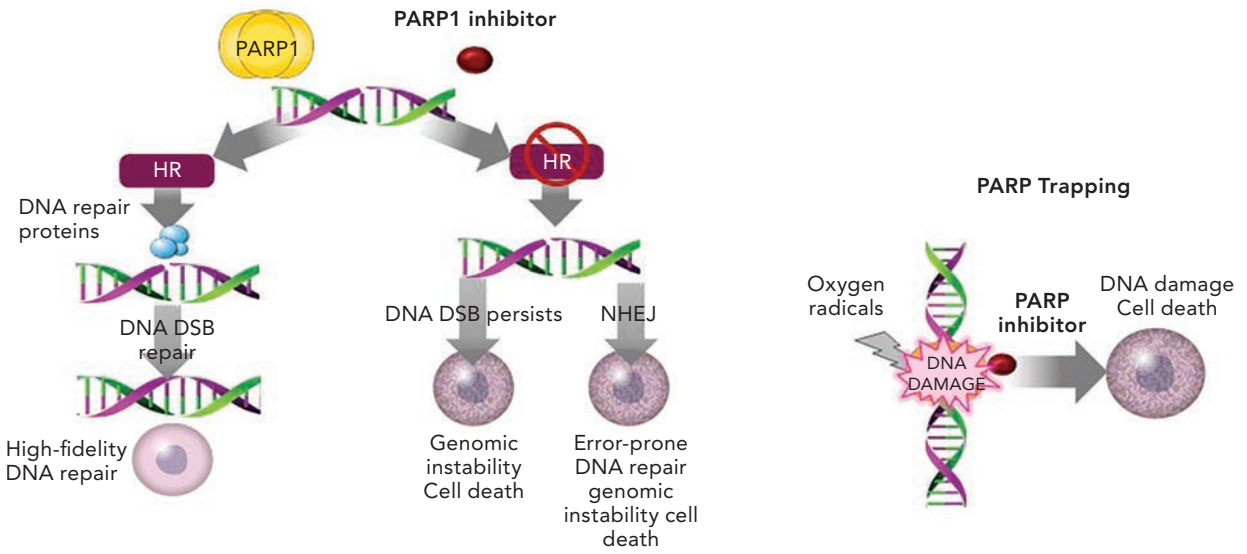
PARP is a key factor in the DNA BER pathway. PARP binds rapidly to single-strand breaks caused by such insults as chemotherapy. Once bound to damaged DNA, PARP modifies itself, producing long branched chains of poly ADP-ribose. PARP recruits repair enzymes and scaffolding proteins to repair the single-strand breaks. With PARP inhibition, single-strand breaks are converted to double-strand breaks which accumulate over time.

In cells with functional BRCA, double-strand breaks are repaired by BRCA via HR. Presence of a BRCA mutation in the tumor cells results in the inability to efficiently repair these double-strand breaks. Double-strand breaks are then only repaired via error-prone NHEJ. Genomic instability and tumor cell death result from NHEJ errors and unrepaired double-strand breaks (Exhibit 2).[5] DNA repair deficient tumor cells, such as those with germline BRCA mutations (gBRCAm), are thus more vulnerable to targeted PARP inhibition.

PARP may be inhibited in a variety of ways. One way is catalytic inhibition to block repair of DNA single-strand breaks (Exhibit 2).[5] Another way is PARP trapping on damaged DNA. PARP inhibition prevents the release of PARP from formed polymers. This inhibits recruitment and binding of other DNA damage repair proteins. In this manner, PARP inhibitors may act as "poisons" by trapping PARP on damaged DNA and preventing DNA repair to promote cell death. PARP inhibition may cause targeted tumor cell death in cancers, including those with DNA repair deficient cells, by synthetic lethality. Synthetic lethality occurs when two genetic lesions, which are individually not lethal, become lethal when combined. That is, cells that are deficient in HR (which is not lethal alone) are hypersensitive to reduction in PARP activity by PARP inhibition.

There are four PARPi on the market (Exhibit 3); however, only olaparib and talazoparib are currently

Exhibit 2: PARP Inhibition in g*BRCA*m Cancer Cells May Result in Targeted Cell Death[5]



PARP = poly ADP ribose polymerase
DSB = double-strand break
HR = homologous repair
NHEJ = non-homologous end joining

FDA approved for BRCA-mutated metastatic breast cancer. Talazoparib has the highest trapping potency and catalytic inhibition of the approved agents.[6,7] Olaparib has the second highest catalytic inhibition and third highest trapping potency.

BRCA mutations occur in both TNBC (24%) and hormone receptor-positive/HER2-negative subtypes (4%).[8-10] BRCA mutation positive breast cancer typically presents with aggressive clinicopathological characteristics compared to general breast cancer population. These include younger age at presentation (<40), increased risk of contralateral BC, higher rates of axillary node involvement, higher tumor grades, higher Oncotype Recurrence Scores, and higher rates of proliferation markers.[11-19]

In a trial of orlaparib in those with gBRCAm metastatic TNBC or hormone receptor-positive metastatic breast cancer which was HER2-negative and who had received two or fewer prior chemotherapy lines in the metastatic setting, the PFS was seven months with olaparib and 4.2 months with chemotherapy.[20] The benefit was greater in those with TNBC compared with those with hormone receptor-positive disease. Olaparib appears to increase the number of long-term survivors with TNBC. Subjects receiving olaparib had better quality of life scores than those receiving chemotherapy.

Talazoparib is theoretically more potent than olaparib. It was studied in gBRCAm metastatic disease in a Phase II trial. This trial included two cohorts of subjects – partial or complete response to the last platinum-containing regimen with disease progression greater than eight weeks following last dose (cohort 1), or three or more prior cytotoxic regimens for metastatic disease but no platinum for metastatic disease (cohort 2).[21] HER2- positive disease was permitted in this trial, but it had to already be resistant to HER2-targeted therapy. The overall response rate (ORR) was 23 percent for BRCA1 and 33 percent for BRCA2. The median PFS was four months and median OS was 12.7 months in cohort 1 and 5.6 months and 14.7 months for cohort 2. These values are about double that which is seen with chemotherapy in heavily pretreated patients.

The Phase III trial of talazoparib compared it to physician choice of chemotherapy in a gBRCAm metastatic population (hormone receptor-positive or TNBC).[22] The majority of subjects had two or fewer lines of prior chemotherapy. Generally, the patient population had rapidly progressive disease and was relatively sick. Median PFS was 8.6 months for the talazoparib group and 5.6 for the chemotherapy group. Patients with brain metastases were allowed in this trial, and there was PFS benefit in this group.

Exhibit 3: Current PARPi FDA Approvals

- **Olaparib:**
  - **2014:** *BRCA*-mutated ovarian cancer who have already received three or more chemotherapy treatments
  - **2017:** maintenance therapy in relapsed patients with platinum-sensitive ovarian cancer
  - **2018:** First PARPi approved for *BRCA*-mutated metastatic breast cancer
- **Rucaparib:**
  - **2016:** advanced ovarian cancer associated with deleterious germline or somatic *BRCA* mutations who have received two or more chemotherapies
- **Niraparib:**
  - **2017:** maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-therapy
- **Talazoparib:**
  - **2018:** *BRCA*-mutated metastatic breast cancer

A secondary endpoint of this trial was OS; interim median OS was 22.3 months for the talazoparib group and 19.5 months for the chemotherapy group. Final OS data has not yet been reported; however, it appears that PARPi are making a difference in the natural history of metastatic breast cancer with gBRCAm.

PARPi adverse effects are similar to what is seen with chemotherapy. The most common adverse effects are anemia, neutropenia, thrombocytopenia, fatigue, nausea, vomiting, and diarrhea. Even with a similar adverse effect profile to chemotherapy, the quality of life in those receiving PARPi tends to be better than those receiving chemotherapy and better preserved over time.

There are some unresolved issues with PARPi treatment of gBRCAm metastatic breast cancer. Resistance to PARPi does occur and research is ongoing to determine the possible mechanisms. Although this class has been studied as second-line or later therapy, there are questions whether it should be used as first-line therapy instead of chemotherapy. Trials to address this issue are ongoing. There are data suggesting an OS benefit in the second-line setting, but the final data are not yet available.

Tumors with BRCA mutations are sensitive to platinum. Veliparib, an investigational PARPi, is being studied in combination with cisplatin for metastatic TNBC, with or without DNA repair issues, or gBRCAm associated disease compared to cisplatin alone. PARPi are also being studied as neoadjuvant therapy of early stage TNBC and gBRCAm disease. An early trial of veliparib in combination with chemotherapy prior to surgery found the PARPi did not add significant benefit to chemotherapy. In addition to not being effective, the adverse effect rates are very high for the combination. The combination of PARPi and chemotherapy can be difficult for patients to tolerate because of the overlap of adverse effects. Talazoparib has been studied as neoadjuvant monotherapy in gBRCAm disease in a trial of 20 women.[23] After six months of oral once a day therapy, pathologic complete responses were seen in 50 percent of those receiving talazoparib; a larger confirmatory trial is ongoing. If the results of the larger trial are positive, the new standard of care for neoadjuvant treatment of gBRCAm disease will be a PARPi instead of chemotherapy.

PARP inhibition is being studied in combination with immunotherapy. Inhibition of PARP in tumor cells carrying BRCA mutations results in accumulating DNA damage and genomic instability. Accumulating DNA damage has the potential to modify tumor immunogenicity (neoantigens), which may make the tumor more sensitive to immunotherapy. Additionally, PARPi upregulates PD-L1 expression in breast xenograft models, which may make checkpoint immunotherapy more effective.[24] In an open-label, multitumor, Phase II basket study of olaparib and durvalumab in gBRCAm metastatic breast cancer, there were good overall response rates but it was not much better than a PARPi alone. A larger trial is ongoing comparing olaparib/durvalumab to olaparib alone as maintenance after chemotherapy. Adjuvant therapy trials and PARPi for treatment of patients with other DNA repair mutations are also being conducted.

Conclusion

The availability of PARP inhibitors has changed the treatment landscape of metastatic breast cancer with BRCA mutations. These agents, which are oral and reasonably well tolerated, improve progression-free survival and likely improve overall survival. Addi-

tional indications for these agents will be coming in the next few years.

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Overcoming Challenges in the Clinical and Economic Management of Primary Immunodeficiency Diseases (PIDD): What Does Managed Care Need to Know About Immunoglobulin Replacement Therapy?

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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

Primary immunodeficiency diseases (PIDDs) are a group of more than 300 diseases caused by defects in the immune system. PIDDs are associated with recurrent infections. The treatment for these diseases is immunoglobulin therapy, which can be burdensome for patients to manage and tolerate. Newer subcutaneous formulations are given at home, primarily by the patient or a caregiver, and are associated with fewer adverse effects and lower overall costs.

Key Points

- Efficacy of available immunoglobulin products is equal.
- Individualized dosing and trough levels are important.
- Tolerability varies by patient, not by product.
- To minimize the risk of severe adverse effects, specific products should be used in certain populations.
- Subcutaneous administration of Ig reduces patient burden and is preferred over intravenous administration.

PRIMARY IMMUNODEFICIENCY DISEASES (PIDDs) can present as specific immune system or innate immune system defects. Specific immune system defects include antibody deficiency syndromes, which predispose those affected to respiratory, gastrointestinal, and cutaneous bacterial infections and cell-mediated immune defects, which leads to severe or persistent viral, fungal, and parasitic infections. Innate or nonspecific immune system issues include phagocytic cell defects, which lead to bacterial and fungal infections, complement defects which lead to Neisseria disease, and disseminated infection, toll-like receptor defects, which lead to staphylococcal and pseudomonas infections, and signaling pathway defects, which increase the risk of bacterial infections. The most common immunodeficiency is antibody deficiency at 78 percent of cases, followed by combined immunodeficiency at 8 percent.[1]

Patients should be referred for a PIDD evaluation when the patient's infection history is outside of the normal range, or meets the criteria shown in Exhibit 1. The goals of an immunologic evaluation are to prevent premature mortality, minimize physical morbidity, maximize the potential for normal physical and psychosocial growth and development, and define the basis of abnormal infection susceptibility to optimize treatment. The content of a first- line immunodeficiency workup is shown in Exhibit 2.

Unfortunately, there is typically a significant time delay in diagnosing PIDD. In one study, there was

Exhibit 1: Referral for a PIDD Evaluation

- When a patient's infection history is outside of the normal range for your practice
- At any age
  - Two or more pneumonias clustered in time
  - Bronchiectasis
  - Infection with signal pathogens
    - Pneumocystis pneumonia
    - Serratia
    - Pseudomonas
  - Invasive fungal infection
  - Two or more invasive bacterial infections
  - Disseminated Neisserial disease
  - Recurrent sinusitis after two or more surgeries
- Infants
  - Persistent bronchiolitis/interstitial pneumonitis at one week or older
  - Chronic diarrhea
  - Recurrent/difficult to treat candida
  - Unexplained rash
- Toddlers and school-aged children
  - Persistent otorrhea after myringotomy tube placement
  - Recurrent otitis media after age four
  - More than four courses of antibiotics per year
- Adults
  - Recurrent bronchitis in non-smokers
  - Infections plus any autoimmune disorders

Exhibit 2: First-Line Immunodeficiency Workup

First Step
- Antibody production defects
  - Quantitate Ig isotypes – IgA, IgG, IgM
    - IgD and IgG subclasses should not be done
    - IgE (allergic antibodies) is helpful
  - Measure specific antibody production
    - Protein (diphtheria/tetanus) antigens
    - carbohydrate (pneumococcal polysacharide) antigen

Second Step
- Cellular immunity
- Granulocyte defects
- Complement defects

at least a five-year delay from the onset of symptoms to the diagnosis.[2] Many think of immunodeficiency as a diagnosis of pediatrics, but 50 percent of diagnoses are made in those over the age of 18. The median age of onset of symptoms is 23 years for males and 28 years for females, but the mean age for diagnosis is 29 years for males and 33 years for females.[2] During the delay from onset of chronic infections to the diagnosis, tissue damage occurs. For example, recurrent sinusitis leads to damage of the sinuses, and recurrent pulmonary infections lead to bronchiectasis.

Untreated PIDD causes significant patient burden via frequent hospitalization, activity limitation, and missed school or work. The diagnosis and treatment of PIDD leads to reduced hospitalizations.[1] Activity limitation and days missed of school or work are also reduced by treatment. Even with treatment, patients can be missing two weeks of work or school yearly because of their disease.

There are also many chronic comorbid conditions with PIDD that contribute to the burden of disease. These include asthma, COPD, arthritis, digestive diseases, malabsorption, and autoimmune diseases. Treatment does not seem to have a major impact on these comorbid conditions.

Undiagnosed PIDD is very costly. In the 12 months prior to starting therapy for PIDD, sinusitis occurred in 35 percent of patients, acute bronchitis in 21.2 percent, and at least one episode of pneumonia in 20.5 percent.[3] These patients had outpatient costs of $22,558, inpatient costs of $12,938, and pharmaceuticals costs of $6,279.[3]

Treatment of PIDD involves replacement therapy with intravenous immunoglobulins. These products are derived from the plasma of healthy people. Immunoglobulins provide several functions, including neutralization and precipitation of toxins; agglutination of bacteria, virus, and pathogenic proteins; complement fixation; and opsonization, which enhances phagocytosis.

The primary efficacy outcome of all immunoglobulin licensing trials as determined by the FDA is the rate of acute serious bacterial infections (aSBI), which includes pneumonia, bacteremia, septic arthritis, osteomyelitis, and abscess. All the commercially available products exceed the standard of less than one aSBI/patient year. Secondary efficacy

Exhibit 3: Routes of IgG Administration

Attribute	IVIG	Conventional SCIG	IGHy
Infusion Frequency	Every 3 - 4 weeks	Daily to every 2 weeks	Every 3 - 4 weeks
Treatment Options	Medical supervision Venous access	Self administration No venous access	Self administration or health care provider No venous access
Relative Dose	100%	137% of IV	100%
Sites per month	1	2 - 16	Typically 1
Systemic AEs	Higher than SCIG	Lower than IVIG	Similar to SCIG
Local AEs	Lower than SCIG	Higher than IVIG	Similar to SCIG

IVIG = intravenous immunoglobulin
SCIG = subcutaneous immunoglobulin
IGHy = subcutaneous immunoglobulin plus hyaluronidase

outcomes include all infections, days of antibiotic therapy, acute care visits, and days missed from work or school. Because there are no head-to-head comparison trials, efficacy comparison between products is not possible. In terms of efficacy for clinical purposes, all of the products are considered equal.

Immunoglobulin dosing has evolved over the years as more experience has been gained in treating PIDD. When first approved in 1981, the dosing was 100mg/kg/month. In 1987, Roifman and colleagues showed, in a subgroup analysis, that fewer pulmonary infections occurred when the IgG trough was maintained at greater than 500mg/dL.[4] This trough value of 500 mg/dL, based on one trial which failed overall, became the standard of care. Several studies since have shown that 500 mg/dL trough is the very lowest limit acceptable, and the more immunoglobulin administered the fewer infections the patient suffers.[5-7] Individualized biologic troughs may be much higher than managed care recommended levels.[6] Currently, the package insert recommendations range from 300mg/kg/month to 800mg/kg/month, but also note that dosing should be adjusted based on clinical outcomes. For every 100 mg/dL increase in immunoglobulin dose, the risk of pneumonia goes down 20 percent.[5] Overall, individual patients require different immunoglobulin levels and individualized dosing to achieve these levels in order to do well.

The FDA requires that new IgG products must demonstrate an area under the time concentration curve (AUC) similar to licensed products to be considered bioequivalent, but instituted this without supporting data that AUC applies to this large molecule product. AUC measurement comes from small molecule pharmacokinetics. Subcutaneously administered products (SCIG) have to achieve an AUC comparable to an intravenous product (IVIG). Bioavailability of SCIG is approximately 63 percent of IVIG. A dose adjustment factor for SCIG of 1.4 times the IVIG dose is mandated by the FDA; however, most immunologists do not apply the adjustment factor when switching patients from IVIG to SCIG. They typically use the same monthly dose when converting patients and then measure levels to adjust the dose. Specialty pharmacy dosing decisions typically adhere to package inserts, which results in higher SCIG dosing than may be necessary.

Immunoglobulins can be given as an intravenous infusion, conventional subcutaneous injection, or IGHy subcutaneous injection (immunoglobulin 10% with recombinant human hyaluronidase 160 units/mL, HyQvia®) (Exhibit 3). The IGHy product has the advantages of self-administration, single-site injection, once a month injection, and minimal adverse effects compared with the other two avenues.

Quality of life index for home SCIG is higher

Exhibit 4: IG Choices for Special Populations

- Hemodynamically unstable neonates – 10% IVIG
- Compensated congestive heart failure – sodium free, 10% IVIG
- Renal compromise, diabetes, or > 55 years old – carbohydrate free
- Poorly controlled migraine – SCIG – if IV, consider giving 50% on the first dose, pre-treat with a triptan
- Hyperviscosity (e.g., MGUS) – 5% product or 10% product using a slow infusion rate

than for hospital or home IVIG.[8] Subcutaneous administration is also less time consuming than IV administration and leads to fewer missed school or work days specifically caused by administration. Thirty-seven percent of patients receiving IVIG report missing work or school to receive the medication compared to 5 percent of those getting SCIG.[1]

Adverse effects are common with Ig therapy. Approximately 90 percent of patients report some type of adverse effect with therapy.[1] Administration rate related adverse effects are the most common cause of tolerability issues. The cause of these adverse effects is unknown but may be high IgG peaks or chronic bacterial colonization which is being 'attacked' by the immunoglobulin. Most common rate related adverse effects are migraine headaches, myalgias, malaise, and fatigue. Less common are fever, diarrhea, rash, cough, chest tightness, and sinus tenderness. These adverse effects are more frequent on the first and second infusion, or after a hiatus in treatment. Injection-site reactions are common with subcutaneous administration. It is not possible to compare the rates with the various products. Patients tend to learn which products they are able to tolerate and which cause administration adverse effects.

Serious, life-threatening adverse events can occur. Renal failure occurs with carbohydrate containing products (particularly sucrose). Risks for renal failure include age, hypertension, renal compromise, and diabetes. In the past, thrombosis occurred because of activated factor 11a contamination; this contaminant has been removed from current products. Some cases of thrombosis still occur and the risk factors are older age, a previous thrombotic event, thrombophilia, and hyperviscosity. Hemolysis, aseptic meningitis, and transfusion-related lung injury can also occur. A risk factor for aseptic meningitis is a history of migraines.

To minimize the risk of severe adverse effects, specific products should be used in certain populations (Exhibit 4). Another way to minimize risk is to alter the dose or infusion rate. For those with a thrombosis history, the dose per infusion and the infusion rate should be limited.

Primary immunodeficiency accounts for 23 percent of the overall use of Ig by unit.[9] Overall, immunoglobulin comprises 8 percent of medical pharmacy spend for commercial plans.[10] Ig spend increased 16 percent from 2015 to 2016 compared with 23 percent for oncology and 55 percent for inflammatory bowel disease.[9] The vast majority of all SCIG for PIDD is given at home; IVIG administration is split among various sites, with clinic and nurse given home infusion the most common. Home health care aided administration grew from 20 percent of total Ig given in 2007 to 40 percent in 2017.[10,11]

Subcutaneous administration is less costly than IV. In a 12-month prospective study of Canadian PIDD patients receiving SCIG at home versus IVIG in the hospital, non-drug costs were $4,187 for hospital-based care versus $1,836 for home care, and physician costs were $744 versus $84 respectively.[12] Home IVIG treatment compared with hospital or clinic-based administration is associated with fewer episodes of bronchitis and pneumonia.[13] Most payers have or will have a site-of-care strategy to try to minimize costs of Ig administration.[14] Managed care plans should encourage the use of SCIG over IVIG and encourage home or office-based IVIG infusion over infusion centers and hospitals.

In addition to site-of-care preferences, preferred drug lists are used by managed care plans to manage costs of immunoglobulins. Importantly, rigid preferred drug lists ignore tolerability data. Patients are exposed to adverse effects that can be burdensome, and they do not like to be told that they have to switch products.

Expertise in managing PIDD is important in achieving good patient outcomes. Board certified immunologists who take care of larger numbers of PIDD patients are better able to individualize care and have better outcomes. Payers should encourage non-academic immunologist experts to care for PIDD patients because care in academic centers is

more costly. Plans can create Ig prescribing "Pre-Check" for experienced, reliable physicians. Overall, optimization of PIDD care is the most cost-effective strategy because it prescribes a tolerable product at an optimal dose and results in better patient adherence, fewer infections, and fewer adverse effects.

Conclusion

Understanding the disease burden of PIDD as well as the burden of care should inform clinical treatment decision making. Tolerability is a major problem for immunoglobulin recipients that impacts the burden of care. Immunoglobulin therapy is best managed by community-based board certified immunologists who can adjust the product selection and dosing to optimize patient outcomes.

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Recognizing Optimal Care Strategies in the Treatment of Major Depressive Disorder

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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

Major depressive disorder (MDD) is mostly treated in the primary care setting. Unfortunately, few patients are treated adequately. Measurement-based care and collaborative care are two effective strategies to improve treatment and successful outcomes.

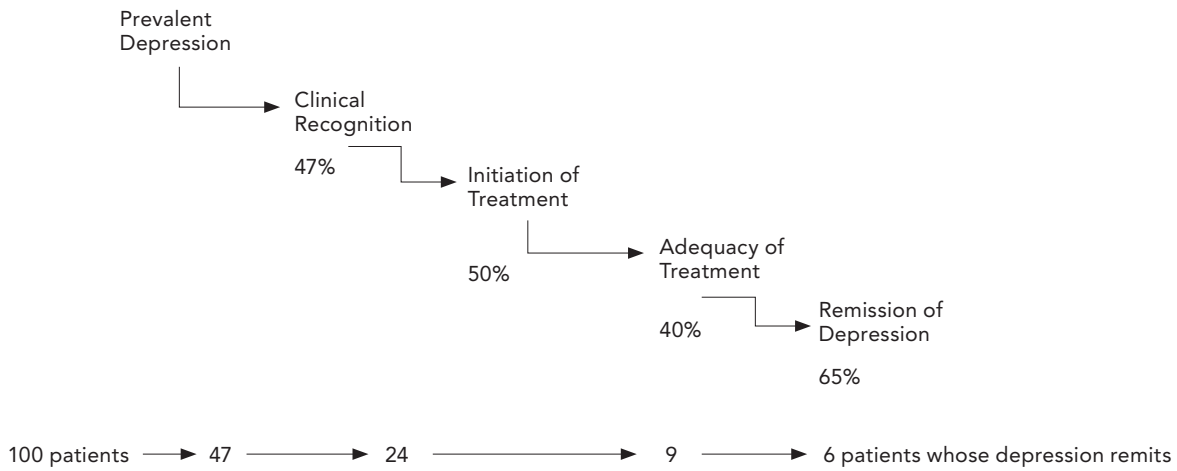
Key Points

- Remission is the goal of treatment.
- Measurement-based care is important for achieving successful MDD treatment outcomes.
- Nonadherence to treatment is a substantial cause for unsuccessful treatment.
- Collaborative care can improve outcomes by helping each step on the depression treatment cascade.

THE BULK OF PATIENTS WITH PSYCHIATRIC disorders are seen and treated in a primary care setting. The appropriate treatment of major depressive disorder (MDD) first requires identification of the person who is depressed, then appropriate treatment has to be instituted, and the patient needs to achieve remission. Unfortunately, MDD is not always recognized or treated appropriately (Exhibit 1).[1] Overall, in the primary care setting, approximately 9 percent of patients with depression receive adequate treatment and 6 percent achieve remission. Recognition of MDD and initiation of treatment are better in psychiatric settings; however, the remission data is not significantly better.

Screening for depression in primary care settings does improve outcomes. The U.S. Preventive Services Task Force (USPSTF) recommends screening for depression in all adults, regardless of risk factors, when staff-assisted depression care supports are in place to assure accurate diagnosis, effective treatment, and follow-up.[2] Thus, systems must be in place to treat the patient with MDD if clinicians are going to screen. A variety of assessment tools are available to help clinicians identify and monitor depression symptoms during treatment. Many of the tools are primarily useful for the research setting; the Patient Health Questionnaire-9 (PHQ-9) can be useful in busy practices, as it is patient administered (Exhibit 2).[3] The PHQ-9 has also been shown to be effective for monitoring efficacy of therapy. Importantly, a positive screening does not make the diagnosis of MDD, but it should be followed up.

Exhibit 1: Depression Treatment Ccascade[1]



Treatment of depression is divided into three phases – acute which lasts six to 12 weeks, continuation for four to nine months, and maintenance which lasts greater than one year. Remission (i.e., complete relief from a depressive episode), rather than merely substantial improvement, is the goal of acute treatment, as it is associated with a better prognosis and better function.[4,5] The continuation phase is to make sure the episode has completely remitted. Maintenance therapy is to prevent relapse. Vigorous treatment of the first episode of depression should be the rule in order to prevent chronic depression. From treatment initiation, clinicians should ensure maximal, but tolerable, doses for at least eight weeks before deciding that an intervention has failed.[5,6] Should the first treatment fail, either switching treatment or augmenting the current treatment is reasonable. Identical remission rates can be achieved in primary and specialty settings when similar evidence-based care is provided (i.e., treatment works).[7]

Most patients will require multiple treatment attempts. With persistent and vigorous treatment, patients with MDD will remit. After one step, about 33 percent will remit; after two antidepressant trials, about 50 percent will remit; after three rounds, 60 percent, and after four rounds 70 percent (assuming patients persist in treatment).[8] The likelihood of remission after two well-delivered medication trials substantially decreases. Such patients will likely require more complicated regimens. Given the thin existing database, these patients are best referred to psychiatrists for more complex treatments.

When the trials of antidepressants were compared in a meta-analysis, no substantial differences in efficacy for MDD were shown.[9] The statistically significant results from meta-analyses were modest and likely not clinically important. There were no differences in quality of life. The general adverse effects are similar among the antidepressants; however, incidence of specific adverse effects can differ significantly among drugs. For example, there are higher rates of nausea and vomiting with venlafaxine than with selective serotonin reuptake inhibitors (SSRIs), and there are higher rates of somnolence with trazodone than with other drugs. Diarrhea occurs more often with sertraline than with other antidepressants, and weight gain is more often with mirtazapine than with SSRIs.

Cognitive behavioral therapy (CBT) is also an option for initial treatment of MDD. CBT and antidepressants show similar benefits.[11] Some patients will respond better to CBT, whereas others will prefer to be treated with a medication. The American College of Physicians (ACP) recommends that clinicians select either cognitive behavioral therapy or second-generation antidepressants to treat patients with major depressive disorder after discussing treatment effects, adverse effect profiles, cost, accessibility, and preferences with the patient. [12] The ACP also recommends that clinicians should assess patient status, therapeutic response, and adverse effects of antidepressant therapy on a regular basis, beginning within one to two weeks of initiation of therapy. Therapy

Exhibit 2: PHQ-9 Symptom Checklist, Scoring, Proposed Treatment Actions[3]

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at All	Several Days	More than Half the Days	Nearly Every Day
a. Little interest or pleasure in doing things				
b. Feeling down, depressed, or hopeless				
c. Trouble falling or staying asleep, or sleeping too much				
d. Feeling tired or having little energy				
e. Poor appetite or overeating				
f. Feeling bad about yourself, or that you are a failure				
g. Trouble concentrating on things, such as reading				
h. Moving or speaking so slowly . . .				
i. Thoughts that you would be better off dead				
Scoring for each item checked in a column	0	1	2	3

PHQ-9 Score	Depression Severity	Proposed Treatment Actions
1 - 4	None	None
5 - 9	Mild	Watchful waiting; repeat PHQ-9 at follow-up.
10 - 14	Moderate	Treatment plan, considering counseling, follow-up and/or pharmacotherapy.
15 - 19	Moderately Severe	Immediate initiation of pharmacotherapy and/or psychotherapy.
20 - 27	Severe	Immediate initiation of pharmacotherapy and, if severe impairment or poor response to therapy, expedited referral to mental health specialist for psychotherapy and/or collaborative management.

should be modified if the patient does not have an adequate response to pharmacotherapy within six to eight weeks of the initiation of therapy.

A major reason antidepressant treatment is not effective is that medications are not used at an adequate dose for an adequate duration of time. Adherence, or lack thereof, is an important part of that. Rates of treatment discontinuation in the first three months of therapy are greater than 40 percent, and 50 percent of patients have stopped therapy within five months.[13] Depression outcomes are worse in patients who do not complete a full course of therapy to remission.[14] Systematic approaches, such as case management or measurement-based care, can improve adherence by 50 percent.[15,16]

Measurement-based care is a consistent strategy to monitor and manage care using objective measurement tools. Clinicians should assess treatment response, adverse effects, and adherence at each visit and at critical decision points to manage aggressively and treat to remission (Exhibit 3).[17] Measurement-based care is feasible and effective in busy primary and psychiatric settings.

At each visit, measures are taken on depressive severity, to assess response, adverse effects, and to assess tolerability. At critical decision points, decisions about dose changes are made. A treatment algorithm is a guide, but clinicians and patients need to make the ultimate decision on dose and antidepressant changes. Remission by the PHQ-9 scale is

Exhibit 3: Measurement-Based Care in MDD[17]

Measurement	Assessment Tools
Depressive Symptoms	• PHQ-9 (Patient Health Questionnaire-9) • QIDS (Quick Inventory of Depressive Symptomatology, Clinician Rated/Self-Report) • BDI (Beck Depression Inventory)
Adverse Effects	• FIBSER (Frequency, Intensity, and Burden of Adverse Effects-Rating)
Adherence	• BMQ (Brief Medication Questionnaire) • MAQ (Medication Adherence Questionnaire)

a score equal to or less than 4. A partial response is a score between 5 and 9 and should prompt consideration of a change. Exhibit 4 shows an algorithm for acute treatment of MDD.

As noted in Exhibit 4, follow-up every four weeks should occur in the acute phase of treatment. Telephone contact in between visits by physician extenders can be made to check on tolerance and adherence. In-person contact is important at critical decision points (4, 8, and 12 week visits), at which time the clinician can change dosing to general categories of low, medium, and high-dose (Exhibit 5).

Other key points for enhancing antidepressant adherence are to involve the patient in treatment decision-making, discuss possible initial adverse effects, and ask about patient preferences for treatment (cost, type). It is also important to discuss the goal for remission and how that will be measured.

Residual symptoms are commonly found in patients achieving remission in which nearly all patients had at least one residual symptom. In one trial, greater than 90 percent of remitters had one or more residual symptom (median, 3).[18] Residual symptoms are linked to increased risk of relapse, faster time to relapse, and significant functional impairment.[15,18] Common residual symptoms are sleep disturbances/insomnia, appetite/weight disturbances, cognitive problems, and lack of energy.

Evidence-based collaborative care models can improve MDD treatment outcomes. One system's approach is integrated care for depression, which addresses the whole person by meeting all of a patient's health needs in one setting. The core principles of effective integrated care include a patient-centered care team providing evidence-based treatments for a defined population of patients using a measurement-based 'treat-to-target' approach.[19,20] A collaborative care model enhances usual primary care by adding two key services – care management support for patients receiving behavioral health treatment and regular psychiatric inter-specialty consultation with the primary care team, particularly for patients who are not improving. In this model, consulting psychiatrists support care managers and primary care providers, provide regular and as needed consultation with a focus on patients who are not improving clinically, and provide education and training for primary care-based providers. They are involved in shaping the provision of mental health care for a large population of patients in primary care, either in person or via telemedicine consultation, or by referral for complex patients. Collaborative care models have been shown to reduce depression symptoms, increase treatment adherence, improve remission rates, improve social functioning, enhance quality of life, improve satisfaction with care, and improve concurrent comorbid conditions while being cost effective.[21-24]

Effective collaborative care models share four core elements:

1) team-driven
2) population-focused
3) measurement-guided
4) evidence-based.

These four elements, when combined, can allow for a fifth guiding principle to emerge: accountabil-

ity and quality improvement. Collaborative care is team-driven, led by a primary care provider with support from a care manager and consultation from a psychiatrist who provides treatment recommendations for patients who are not achieving clinical goals. Other mental health professionals can contribute as well to the collaborative care model. Collaborative care is population-focused, using a registry to monitor treatment engagement and response to care. Collaborative care is measurement-guided with a consistent dedication to patient-reported outcomes and utilizes evidence-based approaches to achieve those outcomes. Additionally, collaborative care is patient-centered with proactive outreach

Exhibit 4: Acute Treatment Algorithm for MDD

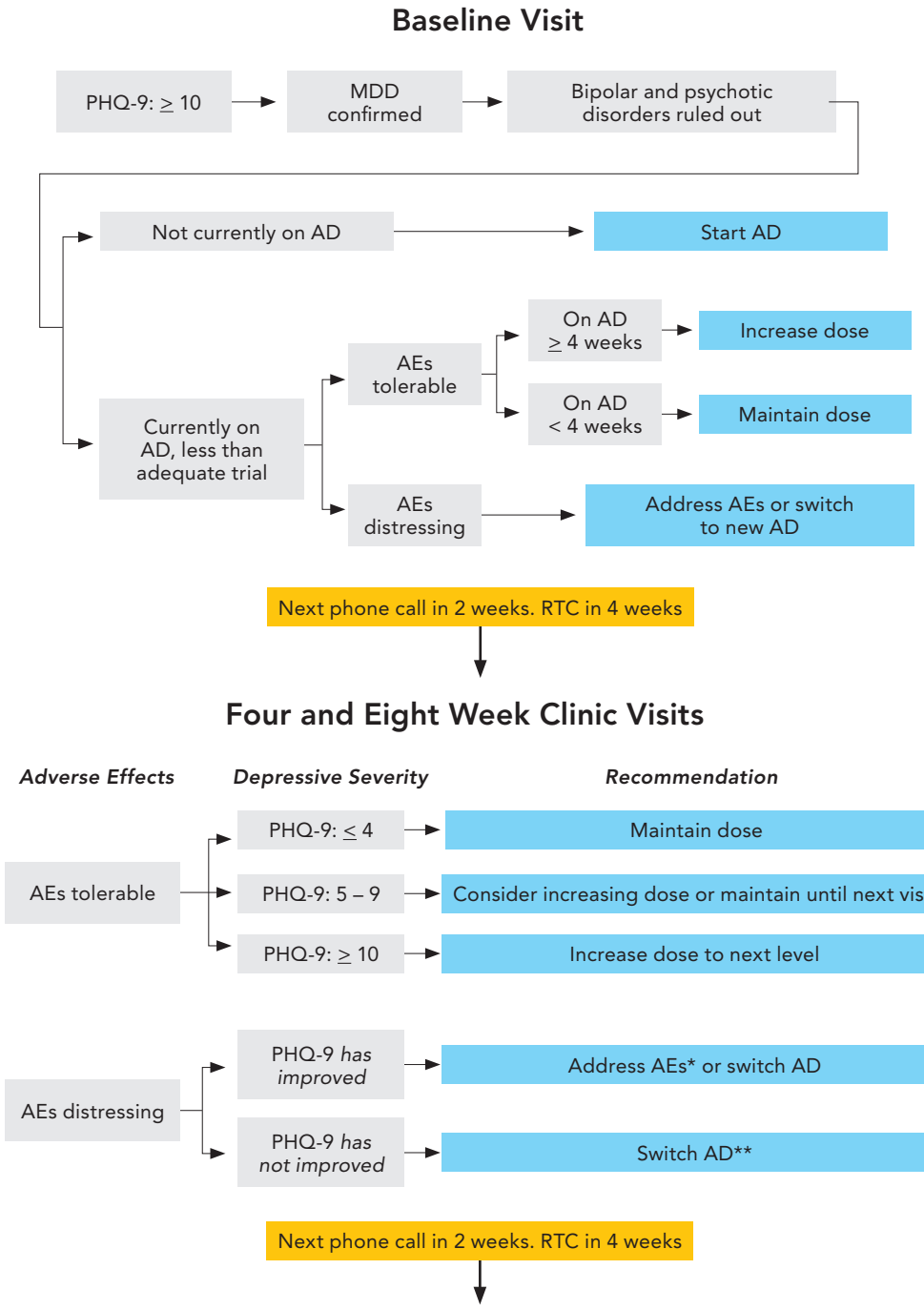
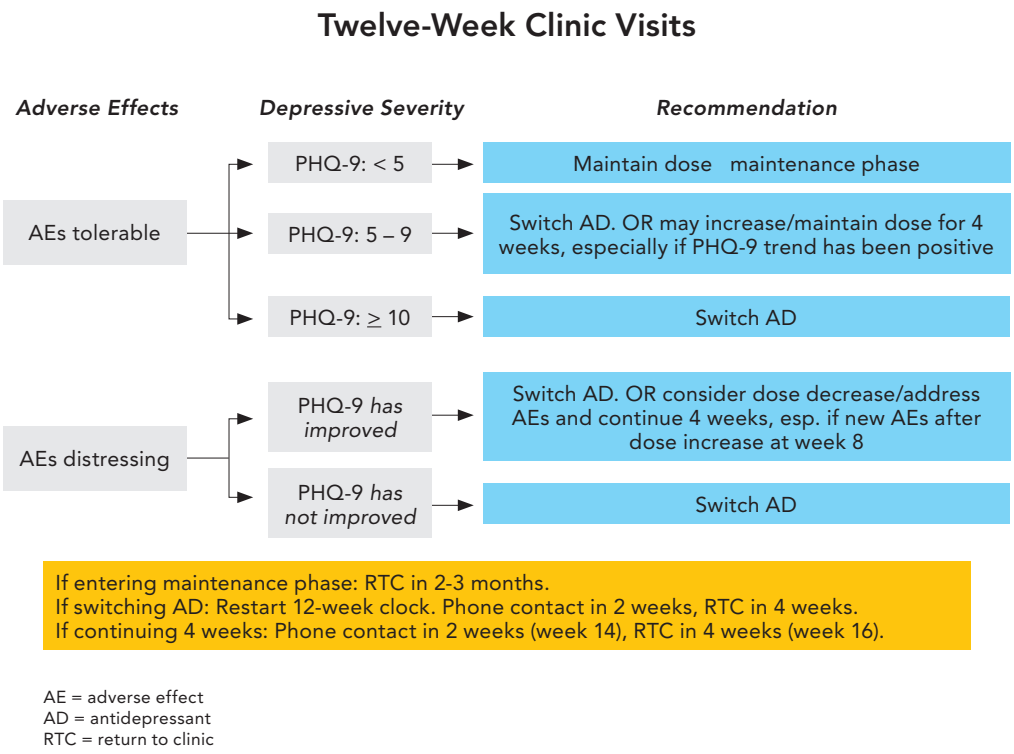


Exhibit 4: Acute Treatment Algorithm for MDD (continued)



AE = adverse effect
AD = antidepressant
RTC = return to clinic

Exhibit 5: Antidepressant Dosing Range

Total Daily Dose Range (mg)				
SSRI	Trade Name	Starting - Low	Middle	High
Fluoxetine*	Prozac	10 qAM X 1 wk, then 20 qAM	40 qAM	60 qAM
Sertaline*	Zoloft®	50 qAM X 1 wk, then 100 qAM	150 qAM	200 qAM
Paroxetine*	Paxil	10 qAM X 1 wk, then 20 qAM	40 qAM	60 qAM
Citalopram*	Celexa	10 qAM X 1 wk, then 20 qAM;	40 qAM	60 qAM
Escitalopram*	Lexapro	10 qAM	20 qAM	20 qAM
Vilazodone	Viibryd®	10 qAM, then 20 qAM,	20 qAM	40 qAM
Vortioxetine	Brintellix	101 qAM	20 qAM	20 qAM
Non-SSRI				
Bupropion SR* Bupropion XL*	Wellbutrin SR Wellbutrin XL	150 qAM X 1 wk, then 100 BID 150 qAM	150 BID 300 qAM	200 BID 450 qAM
Duloxetine*	Cymbalta	30 mg qAM	60 mg qAM	90 mg qAM
Mirtazapine*	Remeron®	15 qHS X 1k, then 30 qHS	45 qAM	60 qHS
Venlafaxine XR*	Effexor XR®	37.5 qAM X 1 wk, then 75 qAM X 1wk, then 150 qAM	225 qAM	300 qAM
Levomilnacipram	Fetzima®	20 qAM X 2d, then 40 qAM	40 qAM	120 qAM

* generic available

to engage, activate, promote self-management and treatment adherence, and coordinate services.

Conclusion

The evidence base for managing depression in the acute phase emphasizes using tools to identify and monitor depression response to treatment. Clinicians should ensure maximal, but tolerable, doses for six to eight weeks before deciding that an intervention has failed. Remission (i.e., complete relief from a depressive episode) is the goal of treatment. Nonadherence to treatment is a substantial cause for unsuccessful treatment. Systematic approaches to disease management, such as measurement-based care, have been shown to improve depression outcomes. Keys to improving adherence include frequent follow-up, involving patients in treatment decision-making, and establishing goals. Collaborative care can improve outcomes by helping each step on the depression treatment cascade.

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Disease-Modifying Therapies in Multiple Sclerosis: Strategies to Optimize Clinical Management

Benjamin M. Segal, MD

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

Summary

Multiple sclerosis (MS) causes significant burden on both a personal and societal level. There has been a revolution in the treatment over the past 20 years. There are now numerous disease-modifying therapies (DMTs) that are changing the natural history of this disease. It is a whole new world for the newly diagnosed patient.

Key Points

- The DMT landscape is complex.
- Treatment choice is further complicated by the considerable risks of some DMT and the need for careful monitoring for adverse effects
- Choice of a specific agent must take multiple factors into account, including efficacy, adverse effect profiles, comorbidities, the patient's willingness to assume certain risks, and the likelihood of long-term adherence.
- There are now approved therapies for primary-progressive and secondary-progressive MS.

MULTIPLE SCLEROSIS (MS) IS A CHRONIC autoimmune demyelinating disease of the central nervous system (CNS), with onset in young and middle adulthood. It is the most common non-traumatic cause of disability among young people in the Western hemisphere. Approximately one million individuals are affected in the United States (U.S.), with an increasing prevalence among non-Caucasian groups.

The natural history of MS is of a relapsing and remitting disease with increasing disease burden and disability (Exhibit 1). Eighty-five percent of cases are relapsing-remitting (RRMS), and the remainder are secondary-progressive disease (SPMS) and primary-progressive (PPMS). Because MS can strike anywhere in the nervous system, the symptoms are quite diverse. The optic nerve, brain, brainstem, and spinal cord are frequently affected, leading to vision issues, ataxia, weakness, paralysis, paresthesia, and bowel and bladder issues. The classic pattern is of relapses alternating with periods of disease remission. During disease remission, the disease is not completely inactive; MRI scans can show new asymptomatic lesions occurring which leave behind scars. These scars reduce an individual's reserve of healthy tissue. Before the disease- modifying treatment era, the majority of patients' disease evolved into a secondary-progressive phase characterized by the gradual accumulation of disability in the absence of acute relapses. After 10 years, about 50 percent of patients had SPMS and by 15 years it is was more than 75 percent. This still occurs in some patients, but to a lesser extent. The diagnostic criteria for MS are shown in Exhibit 2.[1]

The pathologic process of MS is inflammatory damage to the myelin sheath of nerves. Lympho-

Exhibit 1: Natural History of Multiple Sclerosis

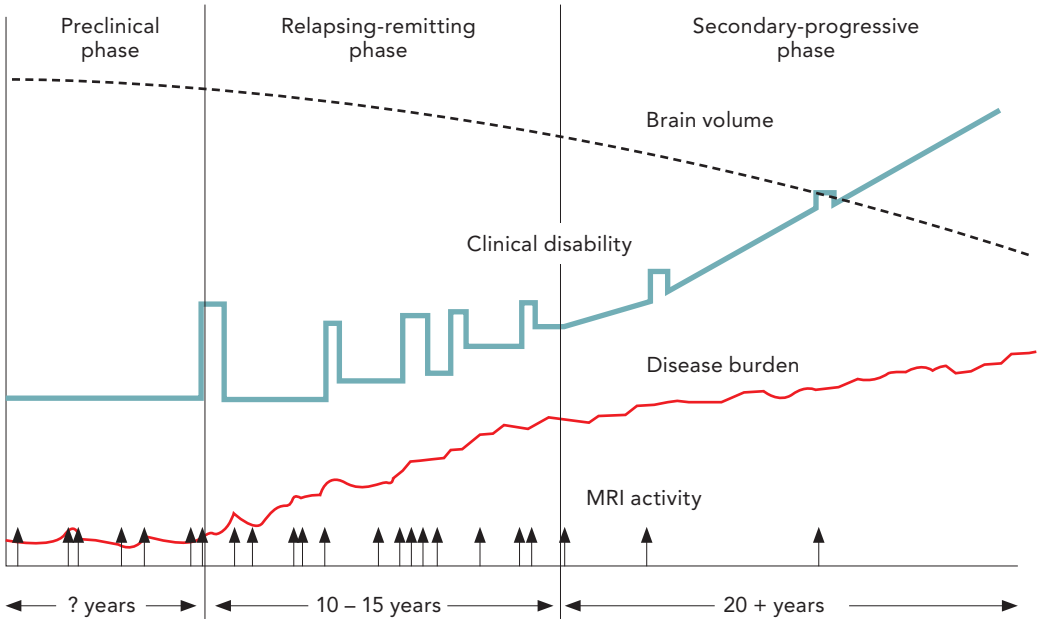


Exhibit 2: 2017 Revisions of the McDonald Diagnostic Criteria[1]

	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of Multiple Sclerosis
≥ 2 clinical attacks	≥ 2	None
≥ 2 clinical attacks	1 (as well as clear-cut historical evidense of a previous attack involving a lesion in a distinct anatomical location)	None
≥ 2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or MRI
1 clinical attack	≥ 2	Dissemination in time demonstrated by an additional clinical attack by MRI or demonstration of CSF-specific oligoclonal bands
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or MRI AND Dissemination in time demonstrated by an additional clinical attack by MRI or demonstration of CSF-specific oligoclonal bands

CNS = central nervous system
MRI = magnetic resonance imaging
CSF = central spinal fluid

cytes, B cells, and T cells inappropriately enter the central nervous system and then recruit other immune cells including lymphocytes and B cells, which attack myelin. Treatment of MS either depletes the immune cells causing the problem or preventing them from entering the CNS.

The goal in MS treatment is to have no evidence of disease activity (NEDA), which will hopefully prevent progression to SPMS. There are multiple FDA-approved DMTs for MS (Exhibit 3). For RRMS, these agents all decrease the annualized relapse rate (ARR), reduce the development of new CNS lesions, and prevent the progression of disability; however, none are cures, and the response rates range

Exhibit 3: Disease-Modifying Therapies

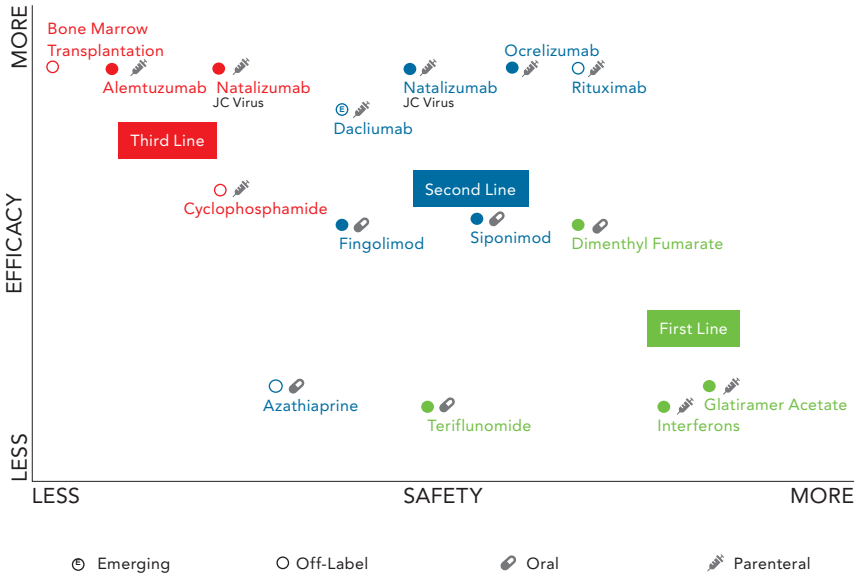
	MOA	Efficacy	Adverse Effects
Alemtuzumab (Lemtrada®)	Depletes CD52+ cells and NKC's.	50% reduction in ARR with efficacy maintained for years after 2 cycles	Autoimmune thyroid disease, ITP, Goodpasture syndrome, infusion reactions, herpes infections
Dimethylfumarate (Tecfidera®)	Reduces oxidative stress by activating nrf-2 transcription.	45% reduction in ARR over 2 years	Flushing, diarrhea, abdominal pain, elevated LFT's and decreased wbc.
Fingolimod (Gilenya®)	Blocks lymphocytes from exiting lymphatic tissue.	54% reduction in ARR over 2 years and decreased disability	bradycardia, macular edema, elevation of LFT's and decreased wbc.
Glatiramer acetate (Copaxane®, Glatopa®)	Synthetic copolymer that simulates MBP and blocks myelin-damaging T cells	29% reduction in ARR over 2 years	Injection site reactions including lipoatrophy, palpitations, chest pain, SOB.
Interferon beta-1b (Betaseron®) Interferon beta-1a (Avonex®) Betaseron beta-1a (Rebif®) Interferon beta-1b (Extavia®) Pegylated interferon beta-1a (Plegridy®)	Induction of anti-inflammatory cytokines and modulates B cell trafficking across the BBB.	30% reduction in ARR over 2 years	Headache, flu-like symptoms, depression, decrease in wbc, elevation in LFT's and injection site reactions in sc drugs.
Natalizumab (Tysabri®)	Inhibits migration of inflammatory lymphocytes across BBB.	67% reduction in ARR and 42% reduction in disability	Infusion reactions, PML, increased risk of common infections (URI, UTI, sinusitis).
Ocrelizumab (Ocrevus®)	Depletes CD20 expressing B cells.	47% reduction in ARR and 40% reduction in disability progression over 2 years	Infusion reactions.
Siponimod (Mayzent®)	Blocks lymphocytes from exiting lymphatic tissue	55% reduction in ARR	Bradycardia, macular edema, elevation of LFT's and decreased wbc.
Teriflunomide (Aubagio®)	Inhibits dihydroorotate dehydrogenase resulting in diminished pyrimidine synthesis in proliferating lymphocytes	33% reduction in ARR over 2 years	Hair thinning, diarrhea, decreased wbc and elevation of LFT's.

MOA = mechanism of action
ARR = annualized relapse rate
SC = subcutaneous
IM = intramuscular
TIW = three times a week
QOD = every other day
QD = every day
BID = twice a day
BBB = blood brain barrier
MBP = myelin basic protein
SOB = shortness of breath
WBC = white blood cells
LFTs = liver function tests
NKCs = natural killer cells
ITP = Immune thrombocytopenic purpura
PML = Progressive multifocal leukoencephalopathy

from 25 to 68 percent. All are approved for RRMS, while only ocrelizumab is also approved for PPMS and only siponimod is approved for active SPMS.

Ocrelizumab was compared to placebo in patients with PPMS and was associated with lower rates of clinical and MRI progression than placebo.[2] The percentage of patients with 24-week confirmed disability progression was 29.6 percent with ocrelizumab versus 35.7 percent with placebo. By week 120, performance on the timed 25-foot walk worsened by 38.9 percent with ocrelizumab versus 55.1 percent with placebo; the total volume of brain lesions on T2-weighted magnetic resonance imaging (MRI) decreased by 3.4 percent with ocrelizumab

Exhibit 4: Disease Modifying Therapies in Multiple Sclerosis: Efficacy versus Safety[7]



and increased by 7.4 percent with placebo, and the percentage of brain-volume loss was 0.90 percent with ocrelizumab versus 1.09 percent with placebo.

Siponimod (Mayzent®) was approved by the FDA in early 2019 for the treatment of relapsing forms of MS to include clinically isolated syndrome, relapsing-remitting disease, and active secondary-progressive disease, in adults. Siponimod binds with high affinity to sphingosine-1-phosphate (S1P) receptors 1 and 5 and blocks the capacity of lymphocytes to egress from the lymph nodes, reducing the number of lymphocytes in peripheral blood. It is an S1P receptor modulator like fingolimod but is more selective for receptors found only on immune cells and will likely cause fewer off-target adverse effects like macular edema and decreased diffusion capacity in the lungs. This agent will still cause bradycardia and first-degree AV block because the same receptors appear on myocytes. In a randomized, double-blind, parallel-group, placebo-controlled, time-to-event study in patients with SPMS who had evidence of disability progression in the prior two years, no evidence of relapse in three months prior to study enrollment, and an Expanded Disability Status Scale (EDSS) score of 3.0 to 6.5 at study entry, siponimod reduced the ARR by 55 percent.[3] Patients do require CYP2C9 genotyping because this affects therapy and dose selection. Those with CP2C9*3*3 genotype should not receive siponimod because of substantially elevated siponimod plasma levels. There are significant adverse effects with every one of the DMTs. Exhibit 3 lists just some of the adverse effects. To monitor for adverse effects, therapy with each DMT requires some type of laboratory monitoring.

Fingolimod, alemtuzumab, ocrelizumab, and natalizumab are more effective than interferon beta 1a, glatiramer acetate, and dimethylfumarate.[4-6] Siponimod is also likely in the highly efficacious category but has not yet been compared to anything but placebo. Safety and lifestyle considerations related to infusion therapies are the reasons not every patient gets started on the highest efficacy agents. Exhibit 4 compares the efficacy and safety of the various agents.[7]

There is an ongoing debate among pundits as to whether all patients should be managed aggressively from the time of diagnosis, as opposed to initiating a DMT with a favorable safety profile (at least in some individuals) and escalating to a high-potency agent as needed. Serious consideration should be given to initiation of a high-efficacy DMT in individuals with poor prognostic factors (i.e., high frequency of clinical relapses/lesion accumulation, relapses with motor dysfunction, poor recovery from relapses). There is increasing evidence supporting transition to a high-efficacy DMT in patients who have breakthrough disease activity on their current agent, or who discontinue natalizumab due to JV virus antibody seroconversion.

The American Academy of Neurology guidelines recommend that clinicians should discuss switching from one DMT to another in people with MS who have been using a DMT long enough for the treat-

ment to take full effect and are adherent to their therapy when they experience one or more relapses, two or more unequivocally new MRI-detected lesions, or increased disability on examination.[8] Clinicians should also discuss a medication switch with patients if adverse effects are intolerable or negatively influence adherence. Clinicians should advocate that people with MS who are stable (i.e., no relapses, no disability progression, stable imaging) on DMT should continue their current DMT unless the patient and physician decide a trial of different therapy is warranted.

Ozanimod is an investigational agent highly selective for S1P receptor subtypes 1 and 5. Like siponimod, it is more selective than fingolimod. Ozanimod is currently investigational; however, it will likely make it to the market before the end of 2019. This agent prevents the exit of CCR7+ lymphocytes from lymph node reducing numbers in peripheral blood. CCR7- lymphocytes, important for viral and tumor surveillance, continue to circulate. Both ozanimod doses demonstrated superiority to IFN β-1a on ARR and MRI endpoints.[9,10] A dose response was consistently demonstrated across these efficacy endpoints. Brain volume, cortical gray matter volume, and thalamic volume loss were slowed compared with IFN β-1a. Overall, ozanimod was generally safe and well tolerated. No subjects had a second degree or higher AV block. Infection risk with ozanimod was comparable to treatment with IFN β-1a. Adverse effects of ALT increased, they were transient, and they generally resolved without study drug discontinuation. These efficacy and safety results demonstrate a favorable benefit-risk profile for ozanimod in RRMS.

Conclusion

With numerous approved medications for the management of relapsing MS on the market, and more coming, the DMT landscape is complex and will become increasingly difficult to navigate over time. Treatment choice is further complicated by the considerable risks of some DMT and the need for careful monitoring for adverse effects. Although there is general consensus that DMT is indicated in individuals with relapsing forms of MS (and certain subgroups with progressive MS), the choice of a specific agent must take multiple factors into account, including efficacy, adverse effect profiles, comorbidities, the patient's willingness to assume certain risks, and the likelihood of long-term adherence. A customized approach is the key.

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Evolving Treatment Strategies in the Management of Melanoma: Expert Perspectives in Immunotherapy

Sanjiv S. Agarwala, MD

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

Summary

The treatment of melanoma has dramatically changed with the approval of checkpoint inhibitor immunotherapy. These agents improve overall survival in the metastatic setting and relapse-free survival and overall survival in the adjuvant setting.

Key Points

- Immunotherapy with checkpoint inhibitors is the standard of care for most patients with metastatic melanoma.
- Either monotherapy or combination immunotherapy can be used in the metastatic setting.
- Checkpoint inhibitors have recently been approved for adjuvant therapy in regionally advanced melanoma.
- For BRAF mutation positive patients, the choice of therapy between targeted agents and immunotherapy is based on clinical judgment.

MELANOMA IS A CANCER OF THE SKIN that begins in melanocytes. Once at metastatic (Stage IV), it is considered incurable. Prior to 2011, the treatment landscape for metastatic melanoma was pretty dismal. Chemotherapy with dacarbazine resulted in response rates less than 10 percent and had no proven impact on survival. High-dose interleukin 2 (IL-2) produced response rates of 16 percent in highly selected Stage IV patients, but it is a difficult therapy to tolerate that requires administration in a specialized, in-patient unit. In addition, there is no randomized trial data supporting its use. High-dose interferon (IFN) was used as adjuvant therapy for high-risk melanoma after surgery, but it has significant toxicity and efficacy concerns.

The treatment of melanoma was revolutionized with the development of immunotherapy using checkpoint inhibitors. T cells can seek out and destroy tumor cells, but their activity is regulated by immune checkpoints to limit autoimmunity. Immune checkpoints, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death 1 (PD-1), lymphocyte activation gene 3 (LAG-3), and T-cell immunoglobulin and mucin protein 3 (TIM-3) function at different phases in the immune response to regulate the duration and level of the T-cell response.[1] The immune checkpoints are essentially the brakes on the immune system. Checkpoint inhibitors take off the brakes and allow the immune system to stay active against tumor cells and also normal cells, which can lead to immune-related adverse effects. An anti-CTLA4 antibody, ipilimumab (Yervoy®), and anti-PD-1 inhibitors, pembrolizumab (Keytruda®) and nivolumab (Opdivo®), are FDA approved for treating melanoma. The combination of ipilimumab and nivolumab is also approved.

Ipilimumab became the standard of care for melanoma when it was approved in 2011. It has been shown

Exhibit 1: Safety of Immunotherapy in Melanoma[9]

	NIVO+IPI (N = 313)		NIVO (N = 313)		IPI (N = 311)	
Patients reporting event, %	Any Grade	Grade 3 - 4	Any Grade	Grade 3 - 4	Any Grade	Grade 3 - 4
Treatment-related adverse effect (AE)	95.8	58.5	86.3	20.8	86.2	27.7
Treatment-related AE leading to discontinuation	39.6	31.0	11.5	7.7	16.1	14.1
Treatment-related death, n (%)	2 (0.6)[a]		1 (0.3)[b]		1 (0.3)[b]	

[a]Cardiomyopathy (NIVO+IPI, n=1); Liver necrosis (NIVO+IPI, n=1).
Both deaths occurred >100 days after the last treatment.
[b]Neutropenia (NIVO, n=1); colon perforation (IPI, n=1).[1]

to provide durable long-term survival in advanced melanoma.[2-4] It is FDA approved for the treatment of unresectable or metastatic melanoma in adults and pediatric patients (12 years and older) and for adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.

The PD-1 immune checkpoint pathway primarily functions during the effector phase of the T-cell response in the peripheral tissue. In healthy tissues, PD-1 is thought to limit the activity of antigen-specific T cells to prevent collateral tissue damage during infection. In cancer, the PD-1 pathway can be exploited by some tumor cells to inactivate T cells.[1] Anti PD-1 is better than ipilimumab frontline in terms of median overall survival (OS); additionally responses are durable even after stopping treatment and the adverse effects tend to be less.[5-6] Nivolumab and pembrolizumab are FDA approved for patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab and for patients with melanoma with lymph node involvement who have undergone complete resection as adjuvant therapy.

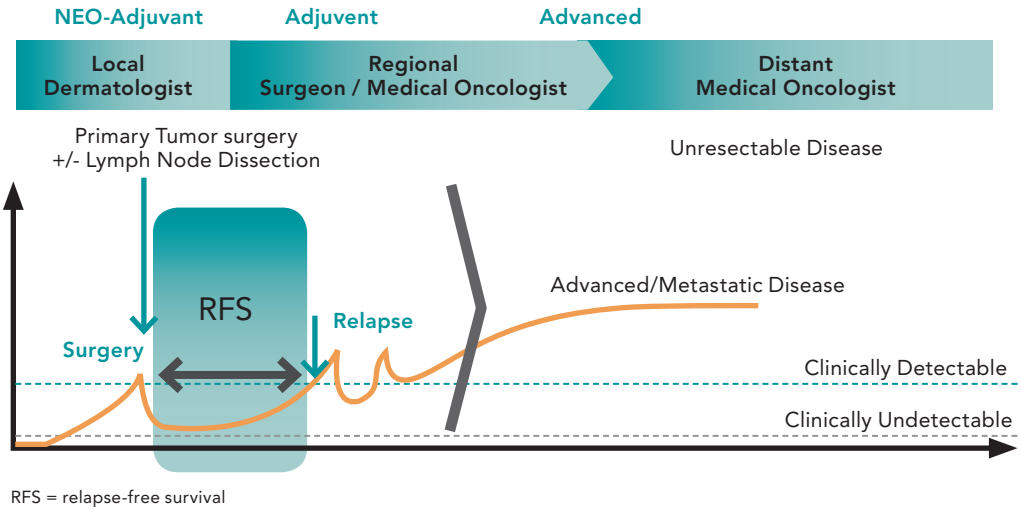
Combining anti-CTLA-4 and anti-PD-1 is even better than either agent alone.[7,8] In the trial of nivolumab and ipilimumab, median progression-free survival (PFS) was 11.5 months with the combination, 6.9 months with nivolumab, and 2.9 months with ipilimumab.[7] Median OS was 38.2 months to not reached, 37.6 months, and 19.9 months, respectively.

A decision point for clinicians is whether to use anti-PD-1 therapy alone or in combination with ipilimumab. Although the efficacy is higher, there is a higher rate of treatment-related adverse effects, adverse effects requiring discontinuation, and treatment-related deaths with combination therapy compared to monotherapy (Exhibit 1).[9] Beyond safety, another factor in the decision between combination and monotherapy is tumor PD-L1 expression levels. Median OS appears better with combination therapy in those whose tumors have low levels of PD-L1 expression. If the tumor has PD-L1 expression greater than or equal to 1 percent, anti-PD-1 monotherapy appears to be the most efficacious in terms of median OS.[10]

Exhibit 2 shows an overview of the melanoma patient treatment journey. Early aggressive intervention may lead to improved long-term cure rates but clinicians need better ways to predict which patients after local or regional treatment. Prognostic factors for assessing risk for recurrence are evolving and becoming more clearly defined. Numerically, most deaths still originate in patients with Stage II and III disease; therefore, adjuvant immunotherapy should be considered.[11] Options for adjuvant immunotherapy are interferon and checkpoint inhibitors. Interferon was the first immunotherapy used in the adjuvant setting; however, because of lack of significant efficacy and major toxicity, it is now no longer used.

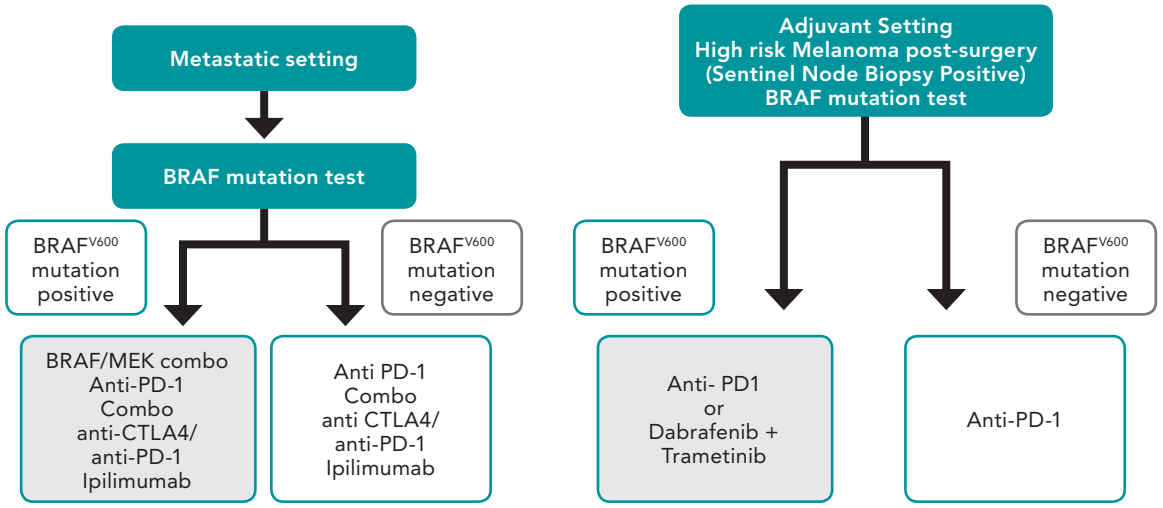
Adjuvant ipilimumab improves relapse-free survival (RFS) and median OS in high-risk resected Stage III disease .[12] Nivolumab has been compared to ipilimumab in the adjuvant setting and produces better RFS than ipilimumab.[13] In this trial the serious adverse effects were less in the nivolumab group. Adjuvant pembrolizumab, given for one year after surgery in high-risk, resected, Stage III cutaneous melanoma, also increase RFS when compared to placebo.[14] Long- term survival data for this trial have not yet been published. As noted previously, all

Exhibit 2: Overview of Melanoma Patient Treatment Journey



RFS = relapse-free survival

Exhibit 3: Selecting Therapy in Metastatic or Adjuvant Setting



three immunotherapy agents are FDA approved for the adjuvant setting.

Questions concerning immunotherapy in melanoma treatment remain. The optimal duration of immunotherapy is unknown. The trials have used various durations. Some data are available to suggest that responses are durable after stopping treatment, but a final answer on length of durability is not known. In an analysis of patients receiving pembrolizumab for greater than 94 weeks, 86 percent who completed two years of therapy were progression free at 20 months after the end of therapy.[15]

Another issue in immunotherapy selection is whether to use a targeted therapy first in those with BRAF positive mutations. Approximately one-half of advanced (unresectable or metastatic) melanomas harbor a mutation in the BRAF gene, with V600E being the most common mutation. Targeted combination therapy with BRAF inhibitors (vemurafenib, dabrafenib) and MEK inhibitors (trametinib, cobimetinib) is associated with significant long-term treatment benefit in patients with BRAF V600-mutated melanoma.[16] These targeted antitumoral therapies have a faster onset of effect than immunotherapy, but resistance does eventually develop and immunotherapy leads to a longer duration of

Exhibit 4: Management of Immune-Related Adverse Effects[15-19]

Severity Grade	Patient Care Setting	Steroids	Other Immunosuppressive Drugs	Immunotherapy and Subsequent Approach
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Not recommended upfront Topical steroids or systemic steroids oral 0.5-1 mg/kg/d for persistent grade 2	Not recommended	Suspend temporarily*
3	Hospitalization	Systemic steroids oral or IV 1 - 2 mg/kg/d for ≥3d then taper over 4 - 6 weeks	Consider for patients with lack of improvement after 2-3d of steroid course Organ specialist advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalization, consider the intensive care unit	Systemic steroids (IV methylprednisolone 1-2 mg/kg/d) and switch to oral prednisone for ≥3d with taper over 4-6 weeks	Consider for patients with lack of improvement after 2-3d of steroid course Organ specialist advised	Discontinue permanently

*Outside of skin or endocrine disorders, where immunotherapy can be maintained

response and tends to be less toxic. Clinicians have to use their clinical judgment to decide between targeted agents and immunotherapy in this setting. Exhibit 3 presents an overview of treatment selection in the adjuvant and metastatic setting. Clinical trial enrollment is also an important option for many patients.

Toxicity management with immunotherapy is very important and is a responsibility of all health care providers. Early reporting by patients with close monitoring and early intervention by health care providers is critical to avoid serious consequences. Clinicians need to provide thorough and continuous patient education about the signs and symptoms of immune-related adverse effects. Signs and symptoms of adverse effects should be assessed before each immunotherapy treatment. Clinicians need to know management algorithms specific to each adverse effect. A general approach based on the adverse effect grade is shown in Exhibit 4.[17-19]

The future of melanoma therapy is to find a new therapeutic partner for anti-PD-1 that is less toxic than ipilimumab and more effective than anti-PD-1 alone. There are numerous other T-cell checkpoints that could be targeted. Another need is an effective way to overcome medication resistance by making "cold" tumors "hot," either by changing tumors not susceptible to immunotherapy, or increasing the amount or efficacy of T cells. Combining immunotherapy with targeted therapy is one option that is being investigated. Better biomarkers for patient selection of immunotherapy are also needed.

Conclusion

Immunotherapy with checkpoint inhibitors is the standard of care for most patients with metastatic melanoma. This is either single-agent anti-PD-1 or combination anti-PD-1/anti-CTLA-4 therapy. Checkpoint inhibitors have recently been approved for adjuvant therapy and are becoming standard of care. For BRAF mutation positive patients, the choice is based on clinical judgment. Future therapies will address better combinations and overcoming resistance.

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Key Insights into the Diagnosis and Treatment of Inflammatory Bowel Disease (IBD)

Siddharth Singh, MD, MS

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

Summary

Biologic therapy has revolutionized treatment of moderate to severe inflammatory bowel disease (IBD). Early combined therapy with biologics and immunosuppressants, along with therapeutic drug monitoring, can both be used to achieve mucosal healing and improve long-term outcomes. Additional targeted biologics and small molecules are in development and are likely to make it to market in next few years.

Key Points

- IBD is an uncommon, chronic condition that has a high cost.
- All immunosuppressive therapies have risks, but the risk of serious consequences may be highest with uncontrolled disease requiring frequent corticosteroids.
- The treatment target in IBD is mucosal healing to modify the natural history of the disease.
- Treatment optimization through risk-congruent early combined immunosuppression and therapeutic drug monitoring helps achieve the treatment target.

INFLAMMATORY BOWEL DISEASE (IBD) IS a relatively low prevalence, high-cost chronic condition. It is estimated to cost $6.8 billion annually. Estimated costs increased 3.3 percent annually from 1996 to 2013. Approximately 54 percent of the costs are from inpatient care, 18 percent from ambulatory care, and 5.5 percent on pharmaceuticals.[1]

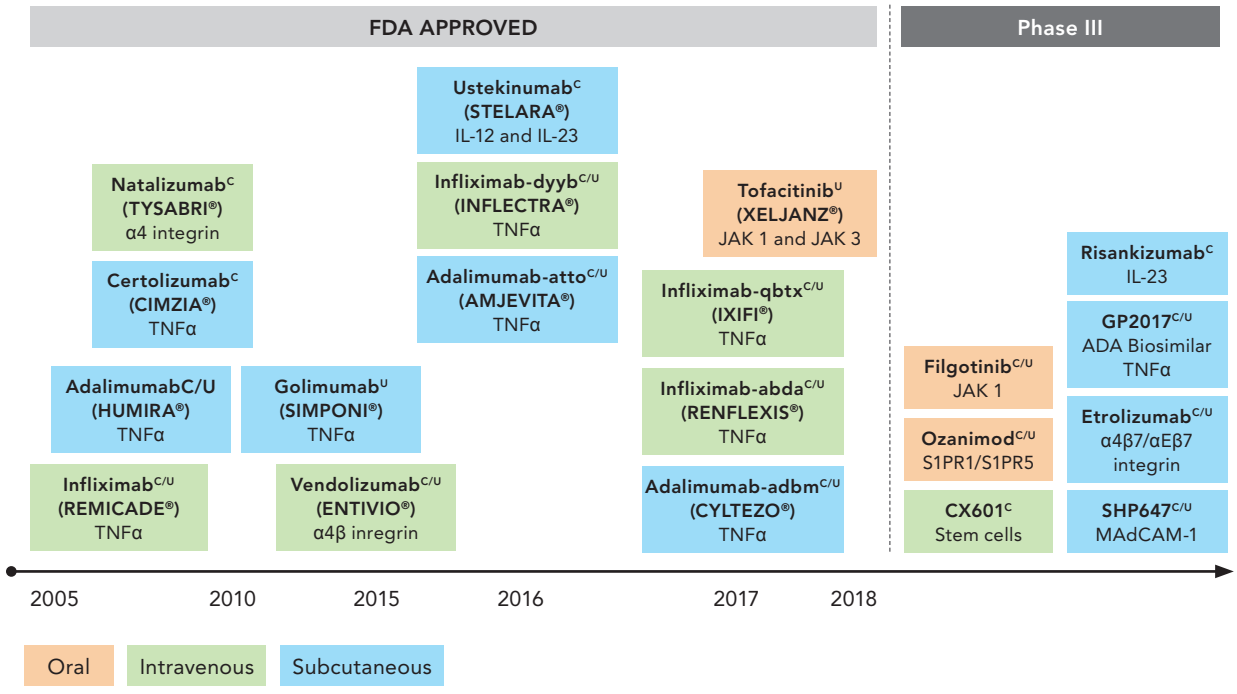
There is a subset of high-cost/high-need patients. These patients have a median of 3.7 days per month in the hospital and have $7,438 per month in costs.[2] The high-cost/high-need subgroup were hospitalized once every two months. Ten percent of patients accounted for 38 percent of all hospitalization costs. The top 20 percent accounted for 55 percent of all hospitalization costs.[2] These patients should be identified by managed care and targeted with case management.

IBD is divided into ulcerative colitis and Crohn's disease and can be mild to severe in intensity. This article focuses on biologics and targeted small molecules which are used to treat moderate to severe IBD. Exhibit 1 shows the currently approved agents for IBD and those which are in Phase III trials. The FDA approved agents are indicated for ulcerative colitis, Crohn's disease, or both.

In 1998, the first biologic approved for IBD was infliximab, an anti-tumor necrosis factor (TNF) monoclonal antibody. Several other anti-TNF agents followed. Natalizumab was the first anti-integrin agent approved, followed by vedolizumab, a more gut-specific anti-integrin. Vedolizumab inhibits leukocyte trafficking into the gut. Anti-interleukin 12/23 and Janus kinase (JAK) inhibitors are also available. Biosimilars for infliximab and adalimumab are also approved for IBD. All of the biologics work by reducing the pathologic inflammatory process.

Treatment of IBD involves induction and maintenance of remission. Exhibit 2 shows estimated rates of induction and maintenance of remission for first-line and second-line treatment in Crohn's disease based on clinical trial data from a network meta-

Exhibit 1: Current Treatment Landscape in IBD



C = Crohn's disease
U = Ulcerative colitis

Exhibit 2: Estimated Rates of INDUCTION and MAINTENANCE of Remission of Crohn's Disease[3]

First-Line			
Agent	Induction of Clinical Remission	Maintenance of Clinical Remission	GRADE Quality of Evidence
Placebo	**16%**	**22%**	-
Infliximab	**53**	**46**	Low
Adalimumab	**42**	**57**	Moderate
Certolizumab pegol	21	38	Low
Vedolizumab	34	38	Moderate
Ustekinumab	34	36	Moderate
Second-Line			
Agent	Induction of Clinical Remission	SUCRA Probability	GRADE Quality of Evidence
Placebo	9%	0%	-
Adalimumab*	25	91%	Low
Vedolizumab	12	35%	Moderate
Ustekinumab	**19**	**71%**	Low

*Adalimumab was selectively studied in patients with PRIOR RESPONSE to infliximab who then develop secondary loss of response or intolerance; patients with primary non-response to infliximab were excluded.

GRADE = Grading of Recommendations Assessment, Development and Evaluation)
SUCRA = surface under the cumulative ranking

Exhibit 3: Estimated Rates of INDUCTION of Clinical Remission and Mucosal Healing in Ulcerative Colitis[4]

First-Line			
Agent	Induction of Clinical Remission	Induction of Mucosal Healing	GRADE Quality of Evidence
Placebo	10%	30%	-
Infliximab	**31**	**59**	Moderate
Adalimumab	16	41	Moderate
Golimumab	23	43	Moderate
Vedolizumab	**32**	**56**	Moderate
Tofacitinib	19	47	Moderate
Second-Line			
Agent	Induction of Clinical Remission	Induction of Mucosal Healing	GRADE Quality of Evidence
Placebo	3%	16%	-
Adalimumab*	4	17	Low
Vedolizumab	10	25	Low
Tofacitinib	**29**	**48**	Moderate

*Adalimumab was selectively studied in patients with PRIOR RESPONSE to infliximab who then develop secondary loss of response or intolerance; patients with primary non-response to infliximab were excluded.

analysis.[3] Anti-TNF agents (infliximab, adalimumab) appear to be the most effective first-line agents for Crohn's disease. Ustekinumab (anti-IL12/23) is probably the most effective second-line agent for Crohn's disease. Although adalimumab appears to have a higher response rate, the adalimumab trial selectively studied in patients with prior response to infliximab who had developed a secondary loss of response or intolerance. Patients with primary non-response to infliximab were excluded. For ulcerative colitis, infliximab and vedolizumab are probably the most effective first-line agents for ulcerative colitis (Exhibit 3).[4] Tofacitinib (an oral Janus kinase inhibitor) is probably the most effective second-line agent for ulcerative colitis. It is important to note that there are few head-to-head trials in IBD and thus some of this is speculation as to the most effective agent. Real-world studies appear to confirm the meta-analysis findings. One showed the superiority of infliximab over adalimumab in ulcerative colitis in terms of hospitalization, major abdominal surgery, and corticosteroid use rates.[5] Exhibit 4 shows data from a real-world comparison of vedolizumab to TNF inhibitors.[6]

Several head-to-head trials are ongoing, including vedolizumab compared to adalimumab for moderate to severe ulcerative colitis, etrolizumab (an investigational anti-integrin) compared to adalimumab for moderate to severe ulcerative colitis, and standard adalimumab versus higher dose adalimumab. Adalimumab may not be as effective as it could be based on the currently recommended dosing. Accordingly, the FDA mandated the dose comparison trial. Results of these trials should help identify how to better position the current biologics.

Several agents are in Phase III trials for IBD. Two small molecule oral agents – filgotinib, a JAK-1 selective inhibitor, and ozanimod, a selective sphingosine 1-phosphate (S1PR1) and 5 (S1PR5) receptor modulator – are the two closest to market. In a Phase II trial of filgotinib, 47 percent of 128 patients treated with filgotinib 200 mg achieved clinical remission at week 10 versus 23 percent of 44 patients treated with placebo.[7] In a Phase II trial of ozanimod, at week 32 the rate of clinical remission was 21 percent in the group that received 1 mg of ozanimod, 26 percent in the group that received 0.5 mg of ozanimod, and 6 percent in the group that received placebo.[8]

In addition to biologics, other immunomodulators are also used to treat IBD. These include thiopurines (azathioprine, mercaptopurine) and methotrexate. Prior to the development of biologics, these agents were used more frequently.

Immunomodulation with thiopurines and biologics does have some risks. Therapy with thiopurines is associated with a risk of serious and opportunistic infections. The risk of these infections is higher with

Exhibit 4: Real-World Observational Comparative Effectiveness: Edolizumab vs. Anti-TNF Agents in IBD[6]

ULCERATIVE COLITIS			
	Vedolizumab	Anti-TNF	Adjusted Hazard Ratio 95% CI
Clinical Remission	**54%**	37%	**1.54 (1.08 – 2.18)**
Steroid-free Remission	49%	38%	1.43 (0.79 – 2.60)
Endoscopic Healing	**50%**	42%	**1.73 (1.10 – 2.73)**
CROHN'S DISEASE			
	Vedolizumab	Anti-TNF	Adjusted Hazard Ratio 95% CI
Clinical Remission	38%	34%	1.27 (0.91 – 1.78)
Steroid-free Remission	26%	18%	1.75 (0.90 – 3.43)

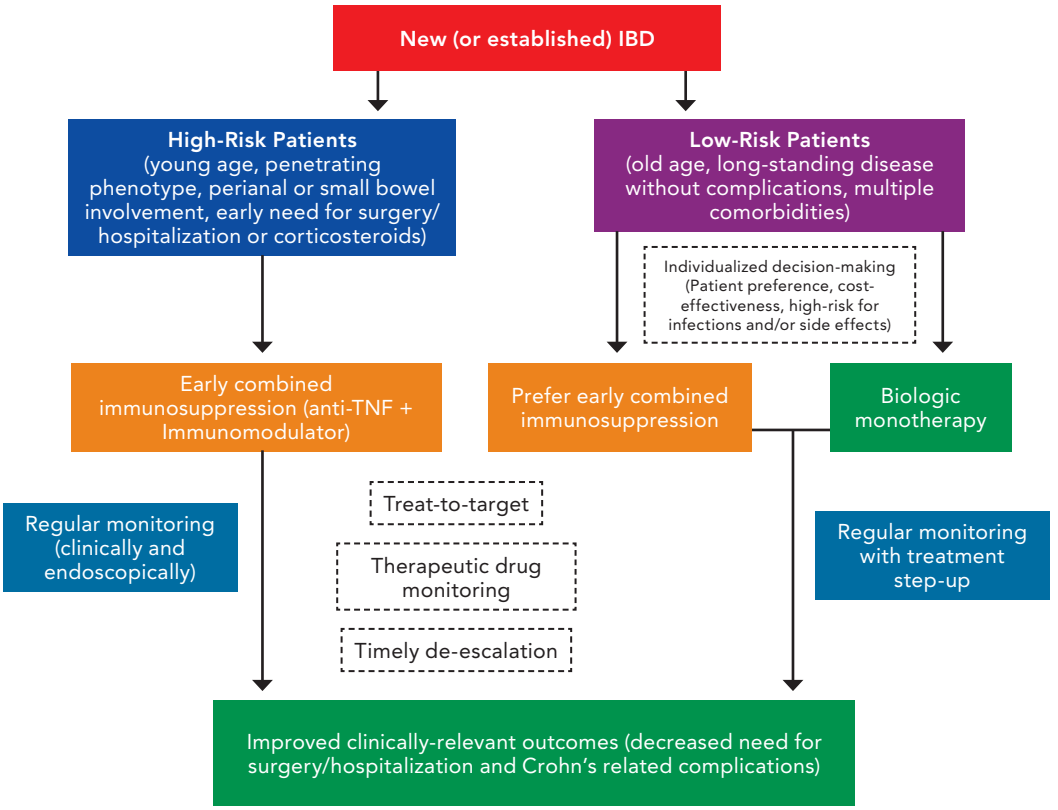
anti-TNF therapy and the highest with combination therapy (biologic + immunomodulators ± corticosteroids).[9,10] Vedolizumab monotherapy is associated with lower risk of serious infections compared with anti-TNF monotherapy; however, the safety advantage is lost when vedolizumab is used in combination with immunomodulators.[6] Importantly, biologics are much safer than long-term use of corticosteroids, There is a higher risk of death, osteoporosis, type 2 diabetes, and cardiovascular events with corticosteroids.[11] Thiopurine monotherapy and anti-TNF monotherapy may be associated with increased risk of lymphoma in patients with IBD, and the risk is highest with combination therapy.[12] The risk of lymphoma without one of these agents is 1 in 5,000, with thiopurine or anti-TNF agent monotherapy 1 in 2,000, and with combination therapy 1 in 1,000. Patients are willing to take on the risks of biologics. In a decision choice analysis, to avoid disease relapse over the next five years, patients were willing to accept a 28 percent chance of serious infection and a 1.8 percent chance of lymphoma.[13] Although there are risks with the medications to treat IBD, uncontrolled IBD and the repeated use of corticosteroids for management, carry the highest risk of infections; achieving and maintaining corticosteroid-free remission is safest.[14,15] Preventive care with appropriate vaccinations and cancer screening also improves safety of pharmacotherapy in IBD.[16]

Treatment targets in Crohn's disease are resolution of abdominal pain and normalization of bowel habits and endoscopic remission (mucosal healing), which is currently defined as absence of ulceration.[17,18] It is important to note that in Crohn's disease symptoms do not correlate well with disease activity. Patients can have minimal symptoms, but have extensive disease on endoscopic exam. Therefore, symptoms alone cannot be used to determine the effectiveness of treatment. Once therapy is started, symptoms should be assessed at least every three months until resolution, and then every six to 12 months. Endoscopy and/or radiologic examination are done six to nine months after starting treatment to assess remission. At this time, biochemical remission (i.e., normalization of markers of inflammation) is not yet a treatment target, but failure of inflammatory biomarkers to normalize should prompt endoscopic evaluation.

Symptoms appear to be better correlated with endoscopic evidence of disease in ulcerative colitis. Treatment targets are resolution of rectal bleeding and normalization of stool frequency and endoscopic remission. Again, biochemical remission is not yet a treatment target. The evolving goal of therapy is a sustained deep remission (clinical, endoscopic, and biochemical remission) for better long-term outcomes of improved quality of life, reduced hospitalizations and surgery, and minimal or no disability.

It is possible to achieve deep remission with an aggressive combination of biologic and immunomodulator therapy. Tight control of newly diagnosed Crohn's disease with high-dose adalimumab

Exhibit 5: Improving Outcomes in IBD with Risk Stratification[22]



and azathioprine has been shown to improve mucosal healing, steroid-free remission, biochemical remission, and deep remission.[19] In this trial, biochemical remission was defined as fecal calprotectin less than 250 μg/g; C-reactive protein less than 5 mg/L; and Crohn's Disease Endoscopic Index of Severity less than 4. Deep remission was defined as Crohn's Disease Activity Index less than 150; Crohn's Disease Endoscopic Index of Severity less than 4 and no deep ulcers; absence of draining fistula, and discontinuation of corticosteroids for eight weeks or more. Mucosal healing has been shown to decrease rates of surgery at one year.[20] The use of algorithmic early combined immunosuppression (biologic plus methotrexate or thiopurine) has been shown to decrease surgery, hospitalization, and serious complications.[21,22]

Therapeutic drug monitoring can be used to optimize treatment in IBD. Some patients do not respond to biologics because of sub-therapeutic drug concentration because of inter-individual variability in drug clearance. Risk factors for sub-therapeutic biologic levels include male gender, high body mass index, high inflammatory burden, concomitant immunomodulators, and anti-drug antibodies. Higher trough concentrations of anti-TNF inhibitors have been shown to improve rates of disease remission.[23,24]

It is imperative to define both the severity and activity of IBD in order to intervene at the right time with the right treatment. The current theoretical model regarding effects of treatment postulates that early intervention may have the greatest potential impact on both the pathologic and clinical course. Exhibit 5 illustrates the use of risk stratification to begin or escalate treatment to achieve the best outcomes.[22]

Conclusion

IBD can be a high-cost chronic condition. Biologic therapy has revolutionized treatment in IBD, and several targeted biologics and small molecules are in development. All immunosuppressive therapies carry risks, but risks may be highest with uncontrolled disease. Treatment targets in IBD have evolved toward achieving mucosal healing to modify the natural history of the disease. Treat-to-target strategies can decrease risk of complications. Treatment optimization through risk-congruent early combined immunosuppression and therapeutic drug monitoring helps achieve the treatment target.

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New Horizons in the Management of Acute Myeloid Leukemia (AML): How Novel Therapies are Changing the Treatment Paradigm

Jeffrey E. Lancet, MD and Timothy Kubal, MD

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

Summary

Within the past five years, the management of acute myeloid leukemia (AML) has dramatically changed from in-hospital chemotherapy to chemotherapy in various settings, with or without oral novel agents. Understanding of the genetic mutations and other mechanisms which drive this disease has led to a growing list of novel therapies. These therapies are improving survival while allowing patients to primarily be treated on an outpatient basis.

Key Points

- AML therapy has moved from only hospital-based chemotherapy to primarily outpatient- based chemotherapy, plus novel agents.
- Agents targeting the two most common genetic mutations – FLT3 and IDH 1/2 – are available.
- A newly approved agent targets a pro-survival protein (BCL2) and is an option in those without FLT3 or IDH 1/2 mutations.
- Liposomal daunorubicin/cytarabine for high- risk AML saves lives when used in suitable patients.

ACUTE MYELOID LEUKEMIA (AML) IS A BLOOD and bone marrow cancer with abnormal myeloblasts, red blood cells, or platelets. Five years ago, the only therapy available for AML was chemotherapy. AML is a very heterogeneous disease. A significant number of molecular subtypes with certain genetic mutations have been identified which affect how the disease behaves.[1] Overall, AML is driven by many different molecular and genetic variations, which can be targeted with specific therapy.

The disease is risk stratified based on cytogenetics and molecular abnormalities for prognostic and therapeutic purposes (Exhibit 1).[2] The overall survival (OS) of patients with AML is largely determined by the initial risk status. The prognosis for those with favorable-risk status is better than those with intermediate- or high-risk status.[3] Other factors in the prognosis include age, type of AML (de novo or secondary), and performance status. Secondary AML arises from myelodysplastic syndrome, myeloproliferative syndromes, or is treatment related. Treatment-related AML is that which develops several years after chemotherapy for a prior cancer. Secondary AML has some specific mutations that are not seen in de novo AML (SRSF2, ZRSR2, SF3B1, ASXL1, BCOR, EZH2, U2AF1, and STAG2). In terms of prognosis, those over the age of 60 have a higher risk of death, as do those with poor performance status and secondary AML.

Exhibit 2 shows the novel agents that are available for targeting specific types of AML. Two of these agents (venetoclax and gilteritinib) were recently

Exhibit 1: NCCN Risk Stratification[2]

Risk Status	Cytogenetics	Molecular Abnormalities
Favorable-risk	inv(16) or t(16;16) or t(8;21) or t(15;17)	Normal cytogetenics: NPM1 mut. without FLT3-ITD or double CEBPA mut.
Intermediate-risk	Normal cytogenetics; +8 alone; t(9;11)	KIT mut., Mutated NPM1 and FLT3-ITD WT NPM1 w/o or low FLT3-ITD
Poor-risk	Complex; monosomal karyotype; -5, -5q, -7, 7q-; 11q23 – non t(9;11); inv(3), t(3;3); t(6;9); t(9;22)	Normal cytogenetics: with FLT3-ITD mut., TP53 mut., Mutated RUNX1, Mutated ASXL1, Wild-type NPM1 & FLT3-ITD

Exhibit 2: Novel Agents for AML

Targets	FLT3	IDH1/2	BCL-2	CD33	Secondary AML
Agents	Gilteritinib (Xospata) Midostaurin (Rydapt) Quizartinib*	Ivosidenib (Tibsovo) Enasidenib (Idhifa)	Venetoclax (Venclexta)	Gemtuzumab ozogamicin (Mylotarg)	Daunorubicin/ Cytarabine (Vyxeos)

* investigational

approved by the FDA. Quizartinib is likely to be approved within the next year.

Fms-like tyrosine kinase 3 (FLT3) mutation is one of the two most common mutations in AML, occurring in about 30 percent of cases. This mutation results in a dysfunctional protein that drives a series of downstream events, leading to leukemia cell proliferation. AML with activated FLT3 mutation is characterized by poor prognosis with only a one to two-year survival and a high relapse rate.[4] Two oral novel agents have been approved for FLT3-mutated disease. Midostaurin, a kinase inhibitor, is approved for newly diagnosed AML with FLT3 mutation and, in combination with chemotherapy, increases median OS by 49 months over chemotherapy alone.[5]

Gilteritinib is a highly potent, selective FLT3/AXL inhibitor with activity in vitro against FLT3-ITD and FLT3-D8354-6, which occur in FLT3-mutated disease that has previously been treated with midostaurin or sorafenib, another kinase inhibitor not FDA approved for treating AML. In a Phase II/III trial, 40 percent of 249 patients achieved a response, with 8 percent achieving complete remission, 4 percent complete remission with incomplete platelet recovery, 18 percent complete remission with incomplete hematologic recovery, and 10 percent partial remission.[6] It was FDA approved in 2018 for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation. This therapy can be a bridge to a curative bone marrow transplant.

Quizartinib is an investigational FLT3 inhibitor that is more potent than midostaurin. This oral, daily regimen has produced close to a 50 percent response rate.[7] The place in therapy for this agent will likely be in relapsed FLT3-mutated AML.

Isocitrate dehydrogenase (IDH) mutations are also a target of novel therapy in AML. IDH is an enzyme in the citric acid cycle. Mutant IDH1 or 2, which occur in 10 to 15 percent of relapsed/refractory AML cases, leads to accumulation of 2-hydroxyglutarate (2HG), which alters DNA methylation and leads to a block in cellular differentiation. Enasidenib is an IDH2 inhibitor that has been studied.in relapsed/

refractory AML. The overall response rate was 38.5 percent and complete response rate was 20 percent.[8] The median OS of 9 months with this agent is very good for the relapsed/refractory population. Those who had a complete response with enasidenib had OS of 19.7 months.[8] Ivosidenib, an IDH1 inhibitor, produced a 30.4 percent complete remission/ complete remission with partial hematological response, 21.6 percent complete remission, and 41.6 percent overall response rate in IDH1- mutated relapsed/refractory AML.[9]

Gemtuzumab ozogamicin, a monoclonal antibody that targets CD33, which is commonly expressed in AML cells, was approved initially in 2001 for relapsed AML in older adults (> 60) who were CD33 positive. It was withdrawn from the commercial market in 2010 amidst concerns for toxicity. Additional clinical trials were conducted with this agent, and it is available again. In newly diagnosed AML, addition of this agent to induction chemotherapy improved OS and relapse-free survival.[10] This agent appears to provide the best survival benefit in those with a favorable cytogenetic profile.[11]

Venetoclax is one of the most exciting agents to come to market for AML. This agent inhibits B-cell leukemia/lymphoma-2 (BCL-2), a pro-survival protein that helps cells live longer by binding to proteins that cause apoptosis.[12] Given in combination with low-dose cytarabine for previously untreated AML in those over the age of 60, it prolonged median OS. Fifty-four percent of the subjects achieved complete remission (CR)/CR with incomplete blood count recovery (median time to first response, 1.4 months) and the median OS was 10.1 months.[13] It is approved by the FDA in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed AML in adults who are 75 years of age or older, or who have comorbidities that preclude use of intensive induction chemotherapy. This agent is also approved for treating chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

A novel intensive chemotherapy using liposomal daunorubicin and cytarabine (Vyxeos®) was approved in 2017 for newly-diagnosed therapy-related AML (t-AML), or AML with myelodysplasia-related changes (AML-MRC). The 100 nm bilamellar liposomes are engineered such that each unit contains 1 mg of cytarabine and 0.44 mg of daunorubicin, which equates to a 5:1 molar concentration ratio. This is an efficient delivery system to provide the most effective killing ratio of the two agents into the cell. A large Phase III study showed a complete response rate of 48 percent versus 33 percent with separate delivery of each agent and improved median OS by 3.6 months in a difficult to treat elderly population.[14] This was the first study of chemotherapy to show a survival benefit in this population. This is an intensive regimen with significant toxicity, so it can only be used in reasonably fit patients.

The old paradigm of treating AML was that patients were treated with chemotherapy in the hospital and either responded or went to hospice. Once the patients who responded relapsed, the cycle was repeated over and over. All the treatment was given in the hospital, and the toxicities were managed while the patient was still hospitalized. The hospital stay was very long (~30 days).

The new paradigm provides many different choices for therapy. Some patients get in-hospital chemotherapy treatment, whereas others receive theirs at an infusion center twice a week for the first few doses until profound neutropenia occurs, and they are then hospitalized for the remaining course. In patients over the age of 60, many are being treated with in-home low-dose chemotherapy, with or without an oral novel agent. With novel agent use, the patient has to see the doctor twice weekly for toxicity management. Patient quality of life is much better now with shorter hospital stays. Previously, patients with newly diagnosed AML were immediately hospitalized and chemotherapy started. Today, treatment is not started until the cytogenetics are done to identify the best treatment.

Because these therapies can be toxic, especially in the first few months of therapy, close monitoring for adverse effects is important to keep patients out of the hospital. Clinicians have to be proactive with regular patient visits or contact. The common adverse effects of cancer treatment are still common in AML treatment – neutropenia, other severe cytopenias, nausea, and constipation. Patients need to know when they should seek care in the emergency department. The novel agents have some unique adverse effects. The most common issues with the FLT3 inhibitors are diarrhea and nausea, but they can cause QT prolongation. Liposomal daunorubicin/cytarabine causes prolonged cytopenias. Gemtuzumab can cause veno-occlusive disease. The most important unique adverse effect is IDH inhibitor differentiation syndrome, which is potentially lethal. Signs and symptoms of this syndrome include dyspnea, fever, pulmonary infiltrates, hypoxia, acute kidney injury, and plural effusion which can be mistaken for pneumonia, fluid overload or heart failure.[15] This syndrome occurs in 10 to 15 percent patients receiving an IDH inhibitor and may occur several months after starting therapy. Treatment is corticosteroids, supportive measures, and holding the IDH inhibitor. There is

a higher risk in those with a high white blood cell count, high blast counts or higher LDH. For those with higher risk, clinicians should consider reducing cell counts with hydroxyurea before starting the IDH inhibitor.

There are decisions to be made when patients are eligible for several different novel agents based on their initial molecular profile. For patients who are suitable for induction chemotherapy, the traditional regimen of daunorubicin and cytarabine (7+3) is usually chosen unless the patient has AML with MRC in which case liposomal daunorubicin/cytarabine is indicated. Novel agents will be added to the traditional regimen. Gemtuzumab is an option for those with favorable-risk cytogenetics. Midostaurin would be added if the patient is FLT3 positive.

For those patients with relapsed/refractory disease that is FLT3 mutated, a FLT3 inhibitor with or without hypomethylating agents (HMA, azacitidine or decitabine) or low-dose cytarabine would be used. The patients would need to be seen twice weekly for follow-up. If IDH1/2 mutation is present, an IDH 1 or 2 inhibitor, with or without a HMA, would be the therapy of choice. With this regimen, a once or twice weekly follow-up would be necessary. For patients with newly diagnosed disease but who are unsuitable for induction with chemotherapy, a clinical trial, venetoclax with azacitidine or decitabine, or an HMA alone are the options. Twice weekly follow-up for adverse effects would be necessary.

In the relapsed/refractory or induction unsuitable setting, choosing to do combination therapy requires a patient who is possibly a transplant candidate, has good social support to do the outpatient visits, can understand the risk of the therapy, and can pay attention to their symptoms so care can be sought if needed. A novel agent such as a FLT3 inhibitor would be used alone when the patient has poor performance status, limited ability to handle logistics of outpatient therapy, limited support in the outpatient setting, or has profound cytopenias or infections with two agents (intolerance).

Conclusion

The treatment paradigm for AML has shifted from primarily long inpatient hospital stays for repeated lines of chemotherapy to combinations of outpatient, in-hospital, and in-home treatment with frequent outpatient visits. Newer targeted agents, alone or in combination with other agents, save or prolong lives with reasonable quality. Appropriate proactive management of the adverse effects of the novel agents is important to keep patients out of the hospital.

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Optimal Approaches to the Treatment of Castration-Resistant Prostate Cancer

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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

A few years ago there were few options for those with advanced prostate cancer, especially castration-resistant prostate cancer. Numerous new agents with various different mechanisms specifically for advanced prostate cancer have been introduced, which are prolonging lives. The best strategy and order for using these agents is still evolving.

Key Points

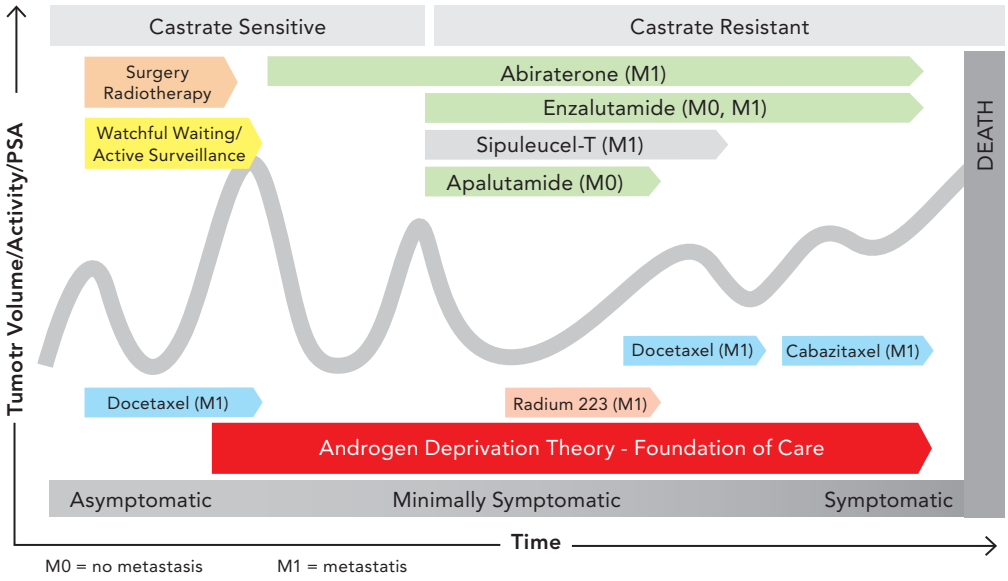
- The backbone of treatment of prostate cancer is depriving the cancer cells of growth-stimulating androgens.
- nmCRPC patients with prostate-specific antigen doubling times of less than 10 months are at high risk of developing metastases or death.
- Apalutamide and enzalutamide are now FDA-approved standard therapy for treating nmCRPC patients.
- The treatment options for mCRPC beyond ADT are numerous, including chemotherapy with docetaxel; bone-targeted therapy with denosumab, zoledronic acid, or radium-223; and immunotherapy with sipuleucel-T.

ACTIVATION OF THE ANDROGEN RECEPTOR (AR) signaling pathway by androgen is critical for prostate cancer tumor growth and disease progression. AR activation is directed primarily by testosterone (T) and dihydrotestosterone (DHT). Reducing availability of T to bind and activate the AR decreases tumor cell proliferation. Lowering production of androgen in the testes, adrenal glands, or tumor cells or blocking the AR are the two ways of reducing availability. Reducing serum T to castrate levels (<50 ng/l) via androgen deprivation therapy (ADT) has become standard of care for patients with advanced prostate cancer.

Prostate cancer cells have a range of androgen sensitivity. They can be hyper- or hypo-sensitive to androgen.[1] Androgen concentrations, above or below the optimal level, are inhibitory, depending on cell sensitivity. Tumors have multiple mechanisms that can overcome androgen deprivation, including AR overexpression, AR mutation, and altered AR activity (post-translational phosphorylation), leading to ADT resistance.

Castration-resistant prostate cancer (CRPC) is defined as a rising prostate-specific antigen (PSA >2 ng/mL higher than the nadir level on ADT with castrate levels of serum testosterone (<50 ng/dL) with or without evidence of metastasis. In terms of metastasis, the patient may have no radiographic evidence of metastasis (known as nmCRPC), or the patient may exhibit radiographic progression (mCRPC).[2-4] Thus, nmCRPC is biologic progression of the disease and mCRPC has evidence of new bone or soft

Exhibit 1: Management of Prostate Cancer[5]



tissue lesions. Prior to recent FDA approvals, there were not great therapeutic options for nmCRPC.

The goals of treating CRPC is to prolong life, prevent pain, prevent complications (skeletal events), prevent decline in performance status, and to preserve quality of life and performance status. ADT is the foundation of treating CRPC and is typically continued even once the patient become castration-resistant (Exhibit 1).[5] While the greater availability of treatment agents benefits patients, the multiple options and sequencing of medications complicates clinical decision-making.

Risk stratifying patients is one option to help select therapy for those with nmCRPC. Prostate-specific antigen doubling time (PSADT) can be used to predict what will happen with these patients.[6] Faster PSADT is linked to shorter time to metastasis in patients with nmCRPC. Patients with PSADT less than 10 months had 12 times greater risk of bone metastasis and four times greater risk of death than those with PSADT greater or equal to 10 months.[7]

First-generation ADT agents are antiandrogens that target the AR (flutamide, nilutamide, and bicalutamide) and luteinizing hormone-releasing hormone (LHRH) agonists/antagonists are second-generation ADT agents. Because of adverse effects, the first-generation antiandrogens are primarily used in metastatic castration-sensitive prostate cancer (mCSPC) in combination with LHRH agonists initially to prevent testosterone flare. The third-generation drugs (abiraterone, enzalutamide, apalutamide) have additional mechanisms and are described as androgen pathway inhibitors (APIs). APIs further reduce activation of AR beyond ADT and thus reduce T levels to almost zero (e.g., abiraterone) and more effectively block AR signaling (e.g., enzalutamide). All APIs require concomitant ADT. APIs were initially approved for mCRPC, and two are now also approved for treating nmCRPC. Efficacy of APIs in mCRPC and nmCRPC demonstrates the importance of the androgen signaling pathway across the disease continuum.

Abiraterone inhibits 17 α-hydroxylase/C17,20-lyase (CYP17), which is involved in androgen biosynthesis. CYP17 is expressed in testicular, adrenal, and prostatic tumor tissues. Abiraterone was first approved in 2011 for mCRPC and then was approved in 2018 for mCSPC. It improves median overall survival (OS) by 4.6 months in those with mCRPC who have had prior chemotherapy and 4.4 months in those who had not had chemotherapy.[8,9] In mCSPC, abiraterone improved OS by 37 percent, failure-free survival by 71 percent, and symptomatic skeletal events by 55 percent.[10] In the newly diagnosed metastatic disease setting, it improved OS by 38 percent, PFS by 53 percent, PSA progression by 70 percent, and symptomatic skeletal events by 30 percent.[11] Concomitant use with prednisone is required to prevent excess mineralocorticoid effects, including hyperkalemia. Abiraterone combined

with prednisone adverse effects include fatigue, arthralgia, hypertension, nausea/vomiting, edema, hypokalemia, hot flashes, and hepatotoxicity.

Enzalutamide is a third-generation AR inhibitor with activity at three places. It blocks binding of androgen to AR, prevents AR from entering cell nucleus, and inhibits AR binding to DNA. It was first approved in 2012 for mCRPC and approved in 2018 for nmCRPC. In the post- chemotherapy mCRPC population, it improves OS by 4.8 months.[12] In the pre-chemotherapy mCRPC population, PFS at 12 months was 65 percent for enzalutamide and 14 percent for placebo, and there was a 29 percent reduction in risk of death.[13] In nmCRPC, median metastasis-free survival was 36.6 months for enzalutamide compared with 14.7 months for the placebo group. The time to PSA progression was 37.2 months for enzalutamide and 3.9 months for placebo; progression occurred in 22 percent vs. 69 percent of patients, respectively.[14] The adverse effects of this agent include seizures (1%), fatigue, decreased appetite, arthralgia, hot flashes, edema, dyspnea, weight loss, headache, hypertension, and dizziness.

Apalutamide is the newest third-generation AR inhibitor that binds directly to the ligand-binding domain of the AR. It was first approved by the FDA in 2018 for nmCRPC. It improved metastasis-free survival (40.5 months vs. 16.2 months with placebo) and PFS (40.5 months vs. 14.7 months).[15] Quality of life was slightly improved in this trial.[16] In another trial in patients with high risk nmCRPC, treatment with abiraterone plus prednisone demonstrated a significant 50 percent or greater PSA reduction with encouraging results for the secondary end points, including the safety of 5 mg prednisone.[17] Apalutamide plus prednisone causes similar adverse effects to abiraterone plus prednisone.

Near complete inhibition of AR activation with APIs produces survival benefit in patients with CRPC and CSPC. Apalutamide and enzalutamide extended nmCRPC patients' median time to metastasis by roughly two years compared to placebo.[14,15] Analyses of OS from the nmCRPC trials with these two agents are pending. Prolonged exposure to novel antihormonal agents prior to metastases adds complexity to the selection of initial and subsequent therapies for treating mCRPC when patients do develop metastatic disease. Additional trials are needed regarding sequencing options with additional lines of therapy once the patient progress from nmCRPC to mCRPC.

Resistance to the third-generation APIs occurs. One reason is the development of AR-V7, a splice variant of the AR. With this variant, the ligand binding domain is no longer on the androgen receptor and APIs will no longer work.[18] Those who are the AR-V7 variant respond to taxane-based chemotherapy.

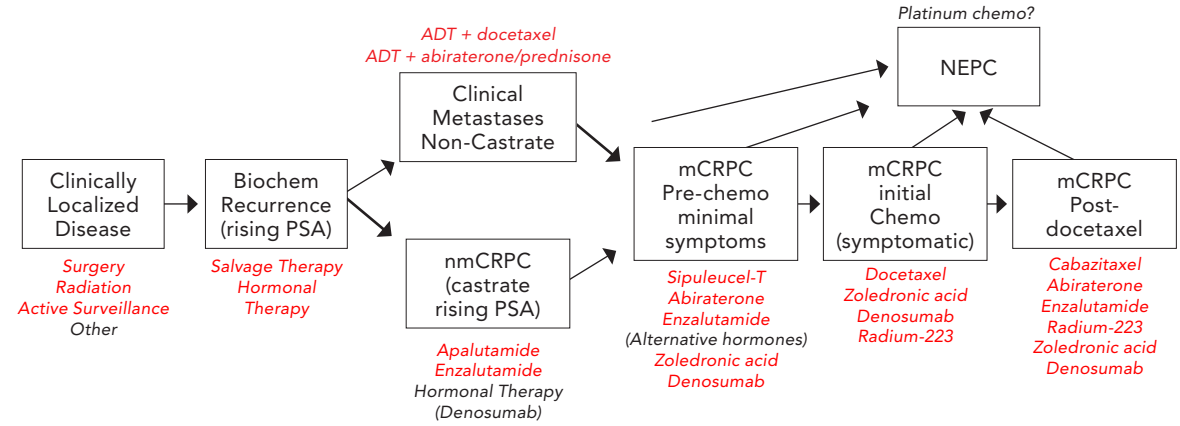
The treatment options for mCRPC beyond ADT are numerous including chemotherapy with docetaxel; bone-targeted therapy with denosumab, zoledronic acid, or radium-223; and immunotherapy with sipuleucel-T. Docetaxel-based chemotherapy improves overall survival for patients with mCRPC and also improves patient-reported outcomes. Bone-targeted therapy decreases skeletal-related events, which are common in metastatic prostate cancer. Radium-223 acts as a calcium mimic, which naturally targets new bone growth in and around bone metastases and has a modest impact on median OS. Sipuleucel-T, an immunotherapy that improved median OS by 4.1 months, is a first-line treatment in patients with asymptomatic or minimally symptomatic mCRPC.

Exhibit 2 summarizes the treatment options for prostate cancer at all stages. Optimal use of chemotherapy, second-generation and third-generation androgen pathway inhibitors, immunotherapy, and targeted alpha therapy to achieve maximum clinical benefit in mCRPC has not been established. There is a lack of head-to-head trials to compare these new agents, and no trials have yet been published comparing combinations to other combinations or monotherapy.[20] As a result, there is no consensus in the current guidelines on the appropriate sequence of the available therapeutic options. The Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence II working group recommends considering therapeutic layering of certain new agents in mCRPC patients when appropriate (Exhibit 3).[20] Therapeutic layering is a clinical point where one or more agent(s) are added onto an existing therapy.

As in other cancers, research is ongoing to discover and target genetic mutations in prostate cancer. DNA repair mutations occur in about 12 percent of men. In cases of prostate cancer with BRCA 1 and 2 mutations or other DNA repair mutations, poly ADP ribose polymerase (PARP) inhibitors are being studied for prostate cancer and are showing significant benefit. Those men who develop early prostate cancer or who have a family history of early prostate cancer, breast cancer, or ovarian cancer should be checked for these mutations.

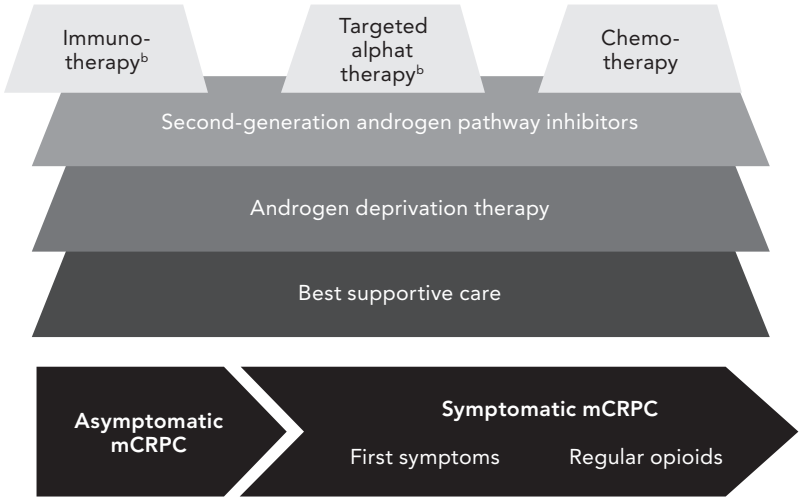
Neuroendocrine prostate cancer (NEPC) is a type of treatment induced androgen deprivation-resistant prostate cancer where the tumor cells have lost their prostate adenocarcinoma phenotype and adopted characteristics of neuroendocrine cells (cells that integrate the nervous system

Exhibit 2: Prostate Cancer Treatment Recommendations



PSA = prostate specific antigen
nmCRPC = nonmetastatic prostate cancer
ADT = androgen deprivation therapy
NEPC = neuroendocrine prostate cancer
mCRPC = metastatic castrate resistant prostate cancer

Exhibit 3: Opportunities for Therapeutic Layering[20]



[a]ClinicalTrials.gov Identifiers: NCT01487863, NCT01981122, NCT02034552, NCT02288247, and NCT02522715
[b]Not eligible if visceral metastasis is present

with the endocrine system by making hormones in response to nerve signals). NEPC is also called treatment-emergent small-cell neuroendocrine prostate cancer (t-SCNC). NEPC is a rapidly progressive disease with metastases to liver and other abdominal visceral organs, and low PSA. Exhibit 4 compares CRPC and NEPC.[21] This subtype of resistant disease is being recognized more frequently, and unfortunately there are not very effective treatments available. Effective treatment of NEPC likely requires a different set of therapies than adenocarcinomas, and numerous studies are under way to address treatment of this subtype.

Beyond choosing the right medication, a multi-

Exhibit 4: Clinical Characteristics of CRPC vs NEPC[21]

	CRPC	NEPC
Bone metastasis	Very common, blastic in nature	May be present and lytic in nature
Liver metastasis	Uncommon	Common
Brain metastasis	Very uncommon (if present, usually dural-based)	Parenchymal brain involvement
Serum PSA level	Generally proportional to disease burden within individuals	Low in proportion to disease burden
Serum neuroendocrine markers (CgA, NSE)	Normal to mildly elevated	Normal to markedly elevated
Response to hormonal therapy	Good	Poor
Pathology	PSA, AR, PSMA+	Synaptophysin, CgA, CD56+
Ectopic hormone production	Rare	Occasionally present
Short interval to progression after initiation of AR-targeted therapy	Uncommon	Common

NEPC = neuroendocrine prostate cancer

disciplinary CRPC clinic can be helpful for managing patients. Urologists, medical oncologists, radiation oncologists, patient navigators, and various support services can all work together to better provide patient care.

Conclusion

Translational therapy has led to real, clinically relevant improvements for patients with advanced prostate cancer. The backbone of treatment of prostate cancer is depriving the cancer cells of growth-stimulating androgens, and this therapy continues through the course of the disease. The most recent advance in therapy is the addition of two agents approved for treating nmCRPC.

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Overcoming Challenges with a Patient-Centered Approach in the Management of Overactive Bladder (OAB)

David R. Staskin, MD

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

Summary

Overactive bladder (OAB) is a common problem that is especially under-recognized and under-treated in men. There are two major classes of oral medication for this condition, with the newer class of beta-3 adrenergic receptor agonists causing fewer adverse effects, especially in the elderly. Clinicians also have to be especially aware of cholinergic burden in the elderly when selecting therapy.

Key Points

- OAB symptoms in men are under-recognized and under-treated.
- Beta-3 adrenergic receptor agonists cause fewer adverse effects than antimuscarinics.
- Antimuscarinics should not be used in the elderly.

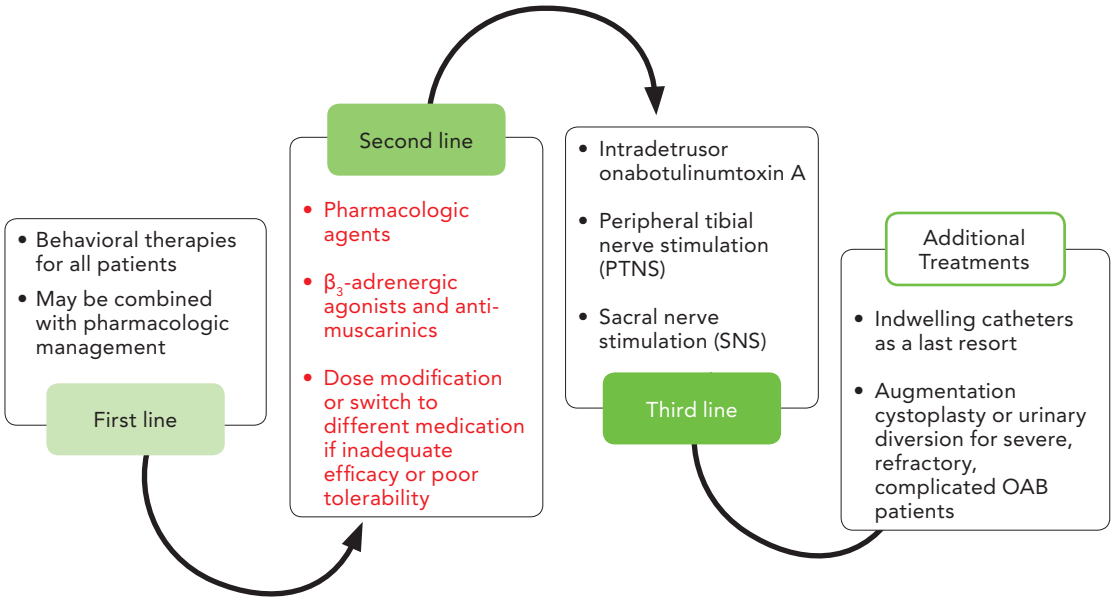
THE INTERNATIONAL CONTINENCE SOciety defines overactive bladder (OAB) as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI) in the absence of urinary tract infection (UTI), or other obvious pathology.[1] OAB symptoms occur due to the failure of the bladder to store urine normally. Overactive bladder can also be seen in combination with stress incontinence and other comorbidities.

Almost thirty million adults aged 40 years and older in the United States (U.S.) are estimated to have bothersome OAB symptoms, at least sometimes.[2] Among Americans aged 40 years or older, approximately 43 percent of women and 27 percent of men have symptoms of OAB, at least sometimes.[3] The prevalence of OAB increases with advancing age in both sexes, with overall prevalence higher in women than in men.[2] In men, OAB prevalence approaches a similar rate to women after the age of 70. Overall, 12.8 percent of women and 10.8 percent of men meet the diagnostic criteria for OAB.[4,5]

OAB symptoms in men are under-recognized and under-treated. In one survey of people with symptoms of OAB, only 45.2 percent of men had discussed their symptoms with a medical provider.[6] In another study, only 25 percent of men diagnosed with OAB received treatment.[7] Part of the reason for under-diagnosis in men may be related to gender-specific differences in the prevalence of various OAB symptoms within the OAB complex. Anatomical and physiological differences between the lower urinary tracts of males and females may help explain these variations. OAB symptoms in males can also be confused with symptoms of benign prostatic hyperplasia (BPH).

OAB has been shown to negatively impact health-related quality of life.[8] Patients with OAB employ

Exhibit 1: OAB Treatment Guidelines[12]



several coping strategies. These may include wearing adult incontinence pads or other absorbent products, using over-the-counter medications, reducing/restricting fluid intake, wearing dark clothes to hide wet spots, trying to urinate on a schedule (timed voiding), and bathroom mapping to be sure they know the locations of all bathrooms in case of urgency. Patients with OAB also avoid doing activities because of concerns about incontinence. Experiencing an episode of incontinence in public is the worst aspect of OAB for many patients.[9]

OAB is also an economically costly condition. The costs include direct medical costs, such as primary care patient visits, specialty physician visits, and medications. Direct nonmedical costs can include pant liners, disposable pads, diapers, latex gloves, and skin protection products. Indirect costs include lost productively. The disease-specific total cost of OAB is estimated at $24.9 to $36.5 billion.[10] Costs are higher among adults younger than 65 years of age, compared with adults 65 years or older.[11] Due to the aging of the general population, the OAB population is projected to increase from 34 million in 2007 to 41.9 million in 2020, thus resulting in an increase in costs.

Before treating OAB, comorbidities and medications that could be causing or worsening symptoms should be ruled out. Excessive consumption of liquids can contribute to frequency and urgency. Urinary incontinence can sometimes be the results of poor ambulation or cognitive problems rather than OAB. Uncontrolled heart failure, diabetes, extremity edema, and sleep apnea can also contribute to nocturia. Neurogenic issues and bladder inflammation or infection can also be causing the urinary tract issues. Overall, other causes of symptoms have to be ruled out and corrected.

The American Urological Association/Society of Urodynamics (AUA/SUFU) treatment guideline recommends behavioral therapies as first-line treatment for all patients (Exhibit 1).[12] For example, pelvic floor exercises can be helpful in suppressing urgency, and decreasing fluid intake after dinner can reduce nocturia. Behavioral therapies can be combined with pharmacologic management for better efficacy. For second-line therapy, beta-3 adrenergic receptor agonists or antimuscarinics are recommended. Dose modification or a switch to a different medication is recommended in the case of inadequate efficacy or poor tolerability. A combination of the two classes is also an option because they have different mechanisms of action. Recommended third-line therapies include intradetrusor onabotulinumtoxinA, peripheral tibial nerve stimulation (PTNS), and sacral nerve stimulation (SNS). Additional treatments may include indwelling catheters and augmentation cystoplasty or urinary diversion for severe, refractory, complicated OAB patients.

Exhibit 2 lists the available oral agents for treating OAB. Antimuscarinics and beta-3 agonists target two distinct neurotransmitter receptors (Exhibit 3). In simple terms, the antimuscarinics block the

Exhibit 2: Pharmacological agents for treating OAB symptoms

Antimuscarinics
Darifenacin
Fesoterodine
Flavoxate
Oxybutynin ER
Oxybutynin IR
Propiverine
Solifenacin
Tolterodine ER
Tolterodine IR
Trospium

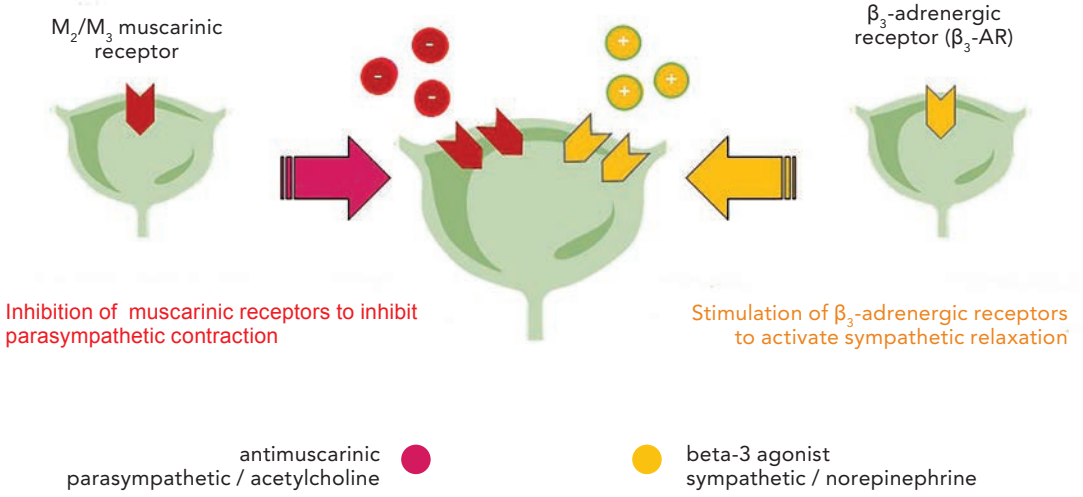
β_3-adrenergic receptor agonist
Mirabegron

In development
Solabegron
Vibegron

desmopressin analogues for nocturia

ER = extended release
IR = immediate release
OAB = overactive bladder

Exhibit 3: Antimuscarinics and Beta-3 agonists Target Two Distinct Neurotransmitter Receptors



"go" receptors in the bladder and the beta-3 agonists stimulate the storage receptors. An extensive review of the randomized trials that evaluated antimuscarinic therapies for OAB (including trials with placebo control groups as well as trials with active treatment comparison groups) revealed no compelling evidence for differential efficacy across medications.[12] One beta-3 adrenergic receptor agonist is currently available (mirabegron), and two more are investigational. There is also a new short-acting desmopressin analogue (Nocdurna®) that is indicated for nocturia. It has been studied in patients with both OAB and BPH to decrease nocturia and can be used in addition to the other two classes.

The majority of patients receiving treatment for symptoms of OAB fail to meet their treatment goals. In a retrospective cohort study of men and women with OAB, 91.7 percent failed to meet their treatment goals with their index antimuscarinic agent over the 24-month follow-up period.[13] Attainment of treatment goals is a strong predictor of treatment satisfaction.[14]

Patient dissatisfaction with the lack of efficacy and adverse effects associated with antimuscarinics leads to high discontinuation rates. Recent studies have found that patients treated with mirabegron have improved treatment adherence and lower discontinuation rates compared to patients on antimuscarinic therapies.[15] Adherence at one year was 31.7 percent with mirabegron and 13.8 to 22 percent with antimuscarinics. Another trial found 64 percent treatment adherence compared with 18.5 to 49.2 percent.[16]

An economic modeling study of the treatment of OAB in the UK found that low-cost generic treatments are not necessarily more cost effective than branded drugs, primarily because a better efficacy and tolerability balance improves both symptom control and persistence.[17] Thus, step therapy programs requiring use of generic antimuscarinic agents may not be cost effective compared with starting with a long-acting branded antimuscarinic or mirabegron.

Because of anticholinergic adverse effects, antimuscarinics are not the best choice for elderly patients.[18] Well over 100 medications are known to have clinically relevant anticholinergic effects and combining these agents leads to significant anticholinergic burden.[19] The Centers for Medicare and Medicaid Services (CMS) has added a poly-anticholinergic medication quality measure. One antimuscarinic may be acceptable for use in the elderly. Studies have shown that trospium does not cause memory issues in the elderly, nor does it enter the central nervous setting when treating OAB.[20-22]

Men are another group which require special consideration. Treatment of both voiding and storage symptoms may be necessary in men for the control of lower urinary tract symptoms (LUTS).[23] Antimuscarinic drugs for OAB are less well studied in males, but have demonstrated efficacy in patients with OAB symptoms without bladder outlet obstruction (BOO). Monotherapy with antimuscarinic drugs has shown limited efficacy in males with OAB and BOO.[23] In a prospective study of 144 men with LUTS, 73 percent of nonresponders to alpha-blocker therapy reported an improvement in symptoms after the addition of an antimuscarinic drug.[24] Traditionally antimuscarinics have been utilized with caution in men because of the possibility of urinary retention related to BOO from BPH.[25] As a beta-3 adrenoceptor agonist, mirabegron relaxes the detrusor smooth muscle during the storage phase of the bladder fill-void cycle resulting in increased bladder capacity with no change to micturition pressure or residual volume. Mirabegron could therefore be used to treat LUTS in males with low risk of acute urinary retention, although more studies are needed to validate the comparative efficacy and safety of beta-3 agonists in combination with antimuscarinics in male patients.

Conclusion

OAB affects the quality of life of patients in major ways. Treatment can be effective, but does require some tailoring in selecting a tolerable medication. Initial use of a better tolerated medication such as mirabegron is likely to result in better success than forcing patients to try multiple different antimuscarinics.

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Clinical Advances in the Treatment of Pulmonary Arterial Hypertension

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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 costly disease, both financially and personally. Survival rates have improved with targeted therapies, but could probably be improved more with aggressive management of medications to achieve low-risk status. Management of these patients requires complex, expensive regimens, which are likely best managed by a multidisciplinary team in a pulmonary hypertension center.

Key Points

- Diagnosis and treatment should be managed by a PAH specialist.
- Patients should be treated aggressively upfront with combination therapy to achieve a low- risk status.
- Triple therapy may be required.
- Therapy should be escalated to achieve low-risk status.
- Prostacyclin targeting agents are likely underused.

PULMONARY HYPERTENSION (PH) IS ELevated pressure in the pulmonary vasculature. There are many different types of PH (Exhibit 1).[1] Group 2 and Group 3 PH are the first and second most common forms of PH. The focus of this article is pulmonary arterial hypertension (PAH).

PAH is a rare form of PH that is progressive and fatal. In contemporary registries, there are 25 to 50 cases per million people, which conservatively equates to 7,500 to 15,000 patients in the United States (U.S.) can be idiopathic, inherited, caused by drug or toxin exposure, or in association with connective tissue disease, congenital heart disease, portal hypertension, or HIV. The median life span after diagnosis before the modern treatment era was 2.8 year. Exhibit 2 shows long-term survival data from the national REVEAL database since time of enrollment in the registry for the various types of PAH.[2] Survival is best for those with drug-related PAH and worst for portopulmonary hypertension. Median survival with modern therapy is now around seven years.

A correct diagnosis is very important because there are effective therapies for PAH; however, these are not effective for other types of PH. In one survey, 39 percent of patients initiated on PAH-specific medication prior to referral to a PAH specialist did not have PAH.[3] Patients also do not get the right tests done for diagnosis.[4] The key test for diagnosis is a right heart catheterization. Many managed

Exhibit 1: World Symposium on Pulmonary Hypertension Classification[1]

1. Pulmonary Arterial Hypertension
   - Idiopathic
   - Heritable
   - Drug- and toxin-induced
   - Associated with:
     - Connective tissue disease
     - HIV infection
     - Portal hypertension
     - Coronary heart disease
     - Schistosomiasis

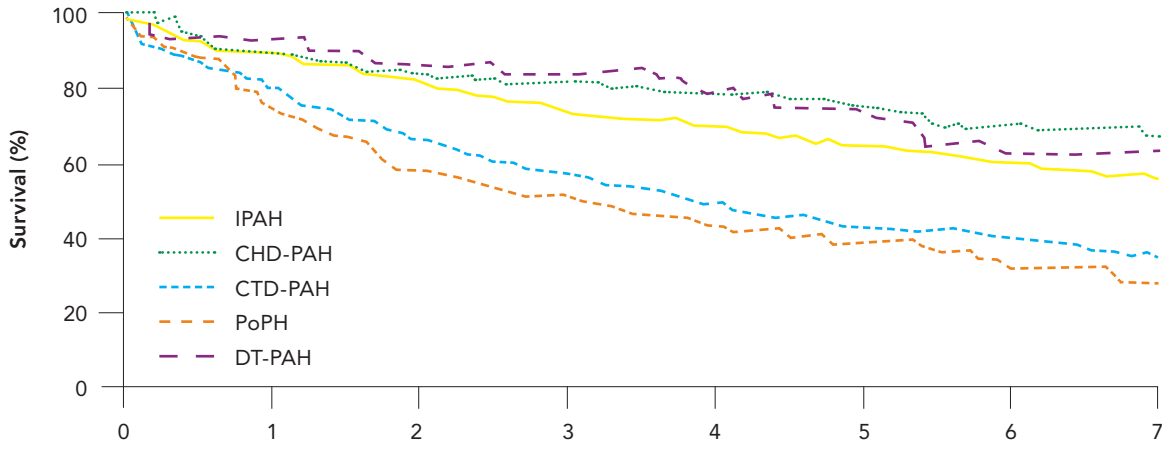
2. PH Due to Left Heart Disease
   - Systolic dysfunction
   - Diastolic dysfunction
   - Valvular disease
   - Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathy

3. PH Due to Lung Diseases and/or Hypoxia
   - COPD
   - Interstial lung disease
   - Other pulmonary diseases with mixed
   - restrictive and obstructive pattern
   - Sleep-disordered breathing
   - Alveolar hypoventilation disorders
   - Chronic exposure to high altitude
   - Developmental abnormalities

4. Chronic Thromboembolic Pulmonary Hypertension

5. PH with Unclear Multifactorial Mechanisms
   - Hematologic disorders (hemolytic anemia)
   - Systemic disorders
   - Metabolic disorders
   - Others

Exhibit 2: Long-term Survival with PAH[2]



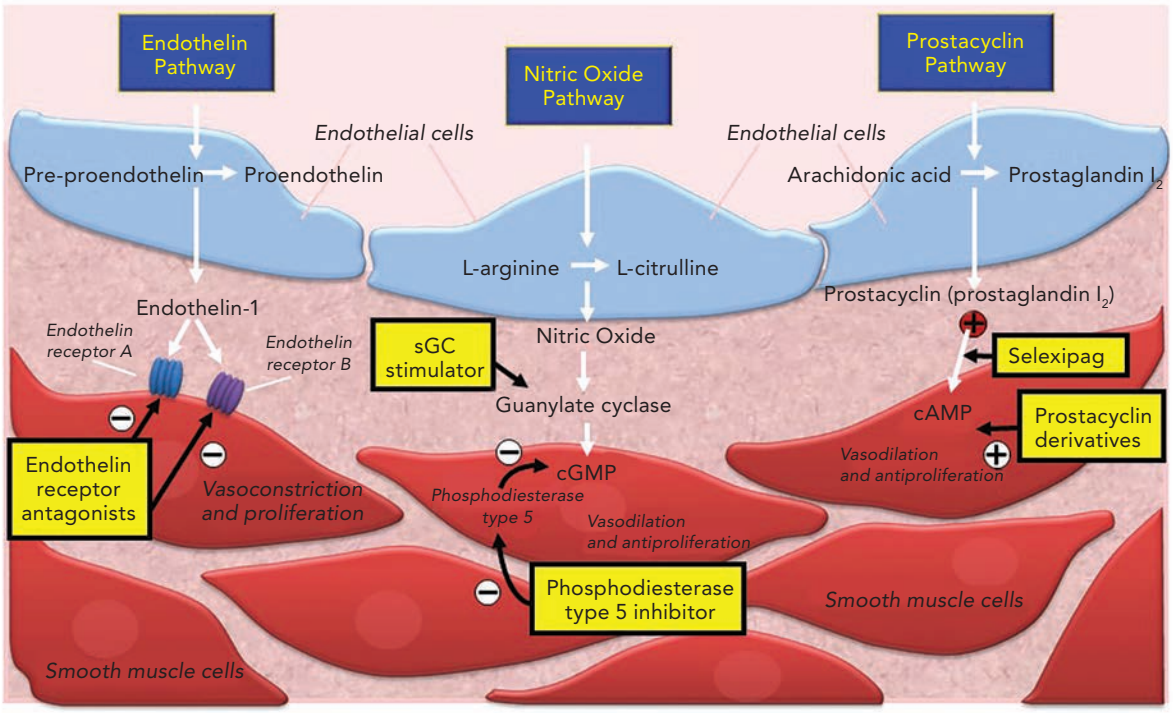
At Risk:				Time from Diagnosis (years)				
IPAH	415	553	600	609	538	415	268	143
CHD-PAH	46	70	107	144	150	138	85	49
CTD-PAH	257	342	344	329	276	203	138	67
PoPH	56	74	70	72	59	42	20	8
DT-PAH	40	57	62	60	55	45	29	21

IPAH = Idiopathic PAH
CHD = Congenital heart disease
CTD = Connective tissue disorders
PoPH = Portopulmonary hypertension
DT = Drugs and toxins

care plans are now requiring this test before any PAH-specific medications can be prescribed, which should help improve prescribing. Because of the difficulty in the diagnosis, it is important that patients with suspected PAH be referred to an expert center for diagnosis. There are over 60 Pulmonary Hypertension Care Centers in the U.S. which have the expertise to care for adult and pediatric patients.

One reason for the short lifespan with PAH is that the diagnosis tends to be made late in the disease process because of the vague symptoms of the disease (shortness of breath, fatigue, chest pain). The mean

Exhibit 3: Treatment Pathways in PAH



time between symptom onset and diagnosis is 27 months. At the time of diagnosis, 70 percent of patients already have significant functional decline and are in the New York Heart Association functional class III or IV.[5] Importantly, presenting functional class predicts survival.[6,7] Thus, early identification before functional decline and treatment to prevent progression of the disease may improve survival.

Certain patients should be screened for PAH. This includes those with scleroderma, systemic sclerosis, cirrhosis, portal hypertension, family history of hereditary PAH, and adults with congenital systemic-to-pulmonary shunts. The patient-centered treatment goals for PAH are to minimize symptoms; maximize functional status; minimize adverse medication effects; minimize treatment burden; avoid hospitalization, transplantation, and complex therapies which are challenging for the patient to manage; maximize quality of life; and increase survival. General treatment steps are to manage heart failure that occurs secondary to the PAH, anti-coagulate certain patients to improve survival, provide long-term oxygen therapy for those with low diffusing capacity for carbon monoxide (DLCO), provide appropriate vaccinations to prevent respiratory illness, counsel patients to minimize high-risk behaviors which further compromise lung function (pregnancy, surgery, hypoxic environments, smoking), and manage any comorbidities. Exercise programs are important for improving physical capacity, but they are rarely covered by insurance. Palliative care and end-of-life planning are also important.

Treatment of PAH involves targeting three different pathways to reduce vasoconstriction and smooth muscle proliferation in the arterioles of the lungs (Exhibit 3). In PAH, the endothelial pathway is up-regulated, whereas the other two pathways are down-regulated. Endothelial receptor antagonists (ERA) decrease the effect of endothelin and include ambrisentan, bosentan, and macitentan. The phosphodiesterase type 5 inhibitors (PDE-5i), tadalafil and sildenafil, and the soluble guanylate cyclase (sGC) stimulator, riociguat, work on the nitric oxide pathway. The ERA, PDE-5i, and sGC stimulator are all oral agents. Selexipag, a prostacyclin receptor agonist, and prostacyclin analogues both increase vasodilation in the arterioles. The prostacyclin analogues are available as oral, inhaled, and continuous intravenous infusion products. The infusion products are the most potent treatment for PAH but cause significant adverse effects and patient burden. Treprostinil is available in all three types of administration routes, including a subcutaneous infusion product. Selexipag is an oral agent, iloprost is only

available by inhalation, and epoprostenol is only available for continuous intravenous infusion. The newest option for delivering prostacyclin analogues is an implantable pump FDA approved in 2018 for treprostinil. The PAH-specific treatments are costly in terms of acquisition costs. The PDE-5i are available generically, but are still $18,000 per year. The prostacyclin analogues are $100,000 and up per year.

There are issues with determining which are the most efficacious PAH therapies because of issues with the clinical trials of the therapies. There are different trial designs, varying study periods, different endpoint definitions, different eras and evolving landscapes, geographic heterogeneity, and a lack of head-to-head trials. The early trials in PAH primarily focused on exercise capacity as measured by the six-minute walk distance. The newer trials have used a combination endpoint of death, hospitalization, lung transplantation, and markers of disease progression.[8,9,10] In the Ambition trial, initial combination therapy (ambrisentan and tadalafil) compared to monotherapy reduced clinical failure (death, hospitalization for worsening PAH, disease progression, and unsatisfactory long-term clinical response) by 50 percent.[8] The majority of clinical benefit was in a reduction in hospitalization. The number needed to treat to reduce a clinical failure event was eight and to avoid a hospitalization was 13. In this trial there was more benefit

Exhibit 4: Treatment Algorithm[13]

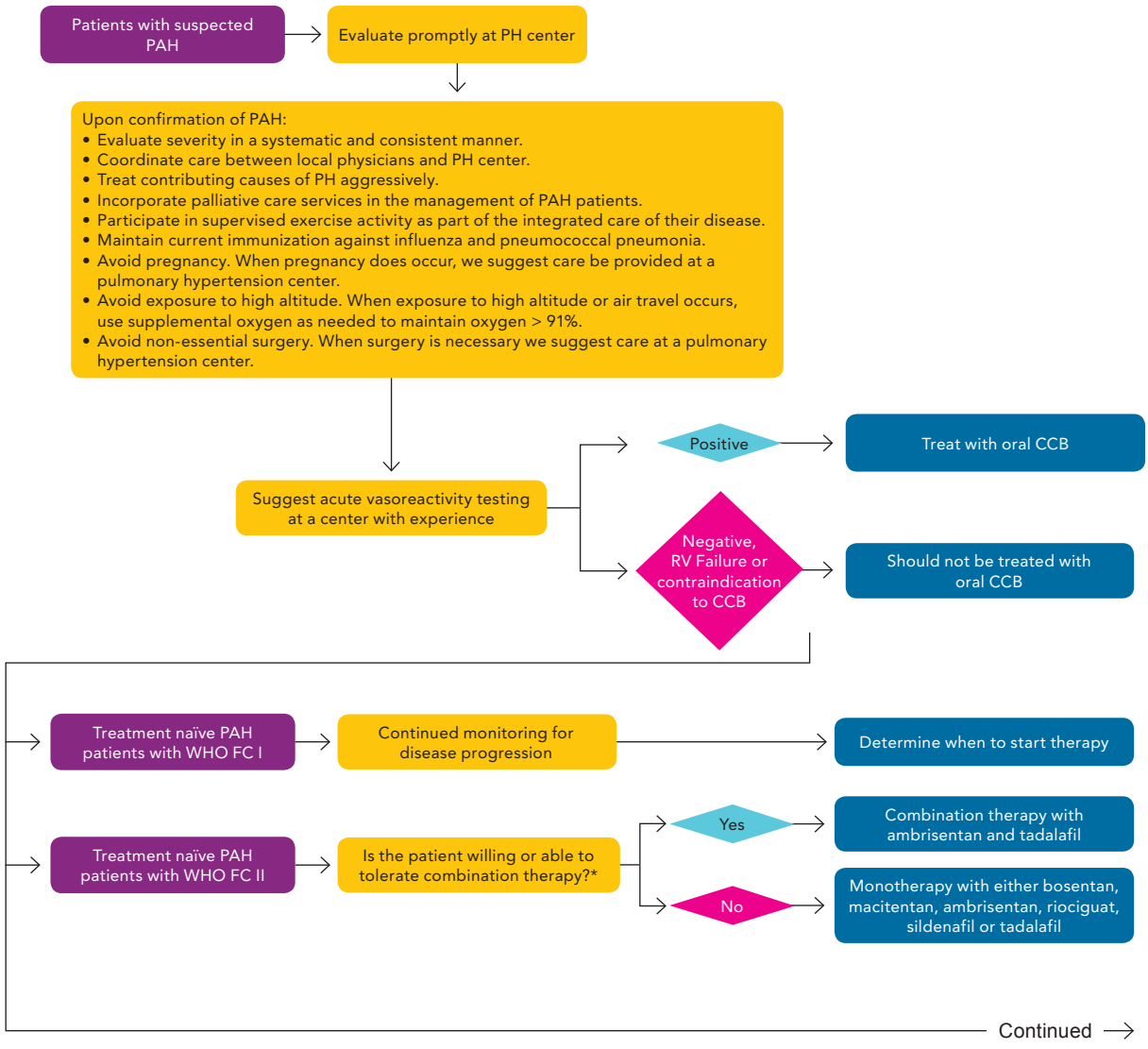
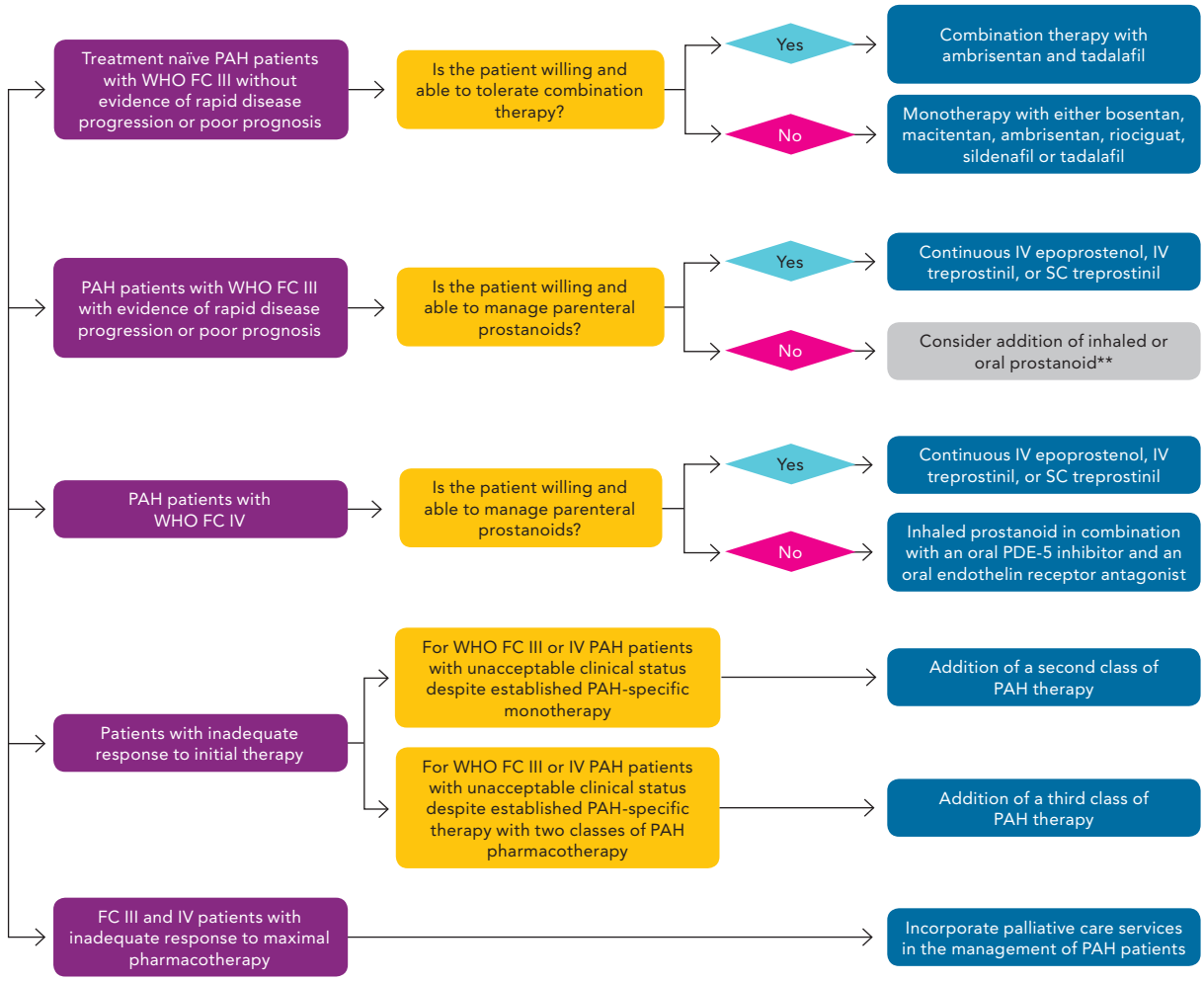


Exhibit 4: Treatment Algorithm[13] *(continued)*



* Combination therapy carries with it costs as well as multiple medications, including the potential for increased adverse events that may be undesirable for some patients. In these situations patients are unwilling or unable to tolerate combination therapy and the panel suggests monotherapy.

** No data available for the use of oral or inhaled prostanoids in patients in whom parenteral prostanoids are indicated, but patient is unable to comply. Thus, we do not have a specific recommendation for this population.

to initial combination therapy in those with better functional class (NYHA class II versus III).

Macitentan monotherapy has also been shown to prolong the time to a PAH-related event or death (any cause) and PAH-related death or hospitalization compared to placebo.[9] Selexipag was shown to improve time to the first morbidity or mortality event compared to placebo in the GRIPHON trial.[10]

Preventing hospitalization is an important endpoint in PAH because hospitalizations give rise to more hospitalizations and post-discharge mortality.[11] All-cause and PAH medical costs decrease significantly following treatment initiation, which is driven primarily by reduction in inpatient admission costs.[12] Median total health care costs (including pharmaceuticals) were higher by about $2,500 after treatment initiation compared to before treatment.

Evidence-based treatment guidelines from the Pulmonary Hypertension Association, the American Thoracic Society and the American Heart Association recommend specific therapies based on functional class.[13] The combination of ambrisentan and tadalafil as initial therapy is recommended for functional class II with low-risk disease. Patients are stratified into low-, intermediate-, and high-risk based on functional class and biochemical markers of disease severity which is used to determine the initial course of action.[14] The guidelines also provide a treatment algorithm (Exhibit 4).[13]

In general, therapy has not been escalated suffi-

ciently in most patients. Data from the national REVEAL registry of PAH patients showed that within six months of death, 35 percent of those in functional class III were on monotherapy and 60 percent were not receiving any intravenous or subcutaneous prostacyclin at the time of death.[15] Of those in functional class IV, 28 percent were on monotherapy within six months of death and 40 percent were not receiving any intravenous or subcutaneous prostacyclin at the time of death.[15] Earlier initiation of prostanoid therapy (within one year of diagnosis) is associated with improved outcomes compared with later initiation, irrespective of the severity of the disease.[16]

An evolving goal of treatment is to treat aggressively upfront with combination therapy to achieve a low-risk category based on measures of function and biomarkers of disease [functional class I/II, six-minute walk distance > 440m, B-type natriuretic protein (BNP) < 50 ng/L or N-terminal-pro hormone BNP (NT-proBNP) < 300 ng/L, right atrial pressure < 8mm Hg, cardiac index ≥ 2.5 L/min/m^2, and mixed venous oxygen saturation (SvO_2: > 65%)]. Hopefully, this aggressive treatment will slow progression and continue to improve survival.

Therapies in development are improving on the currently available agents. A dry powder inhaler and a subcutaneous formulation that reduces adverse effects are both under development for treprostinil. A once-a-day prostanoid receptor agonist (ralinepag) is close to market approval. Final data from a trial of upfront triple oral combination therapy will likely be presented in 2019. Investigational agents are moving beyond vasodilator therapy to target other pathways and even to target genetic mutations that lead to inherited PAH. Other studies are looking at repurposing already approved medications such as carvedilol to mitigate sympathetic activation and ventricular dysfunction that result from PAH.

Conclusion

Diagnostic complexity and infrequency of PAH continue to challenge its proper and timely diagnosis. Treatment paradigms continue to evolve with initial upfront combination therapy and aggressive management of medications to achieve low-risk status. The prostacyclin pathway agents are underutilized and probably should be instituted earlier in the disease process. Treatment goals are being redefined as reducing hospitalization, preventing disease progression, and reducing treatment burden.

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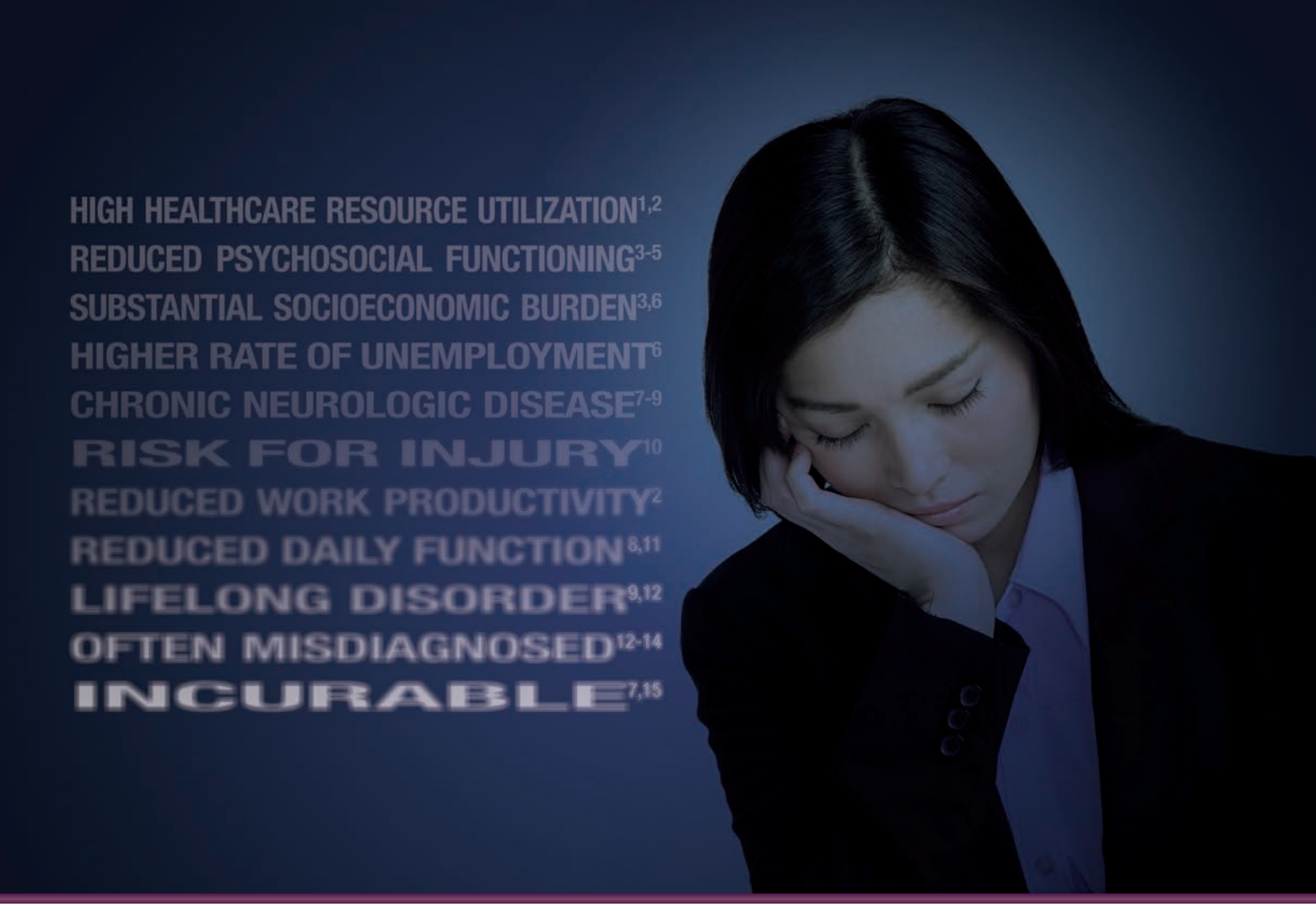

Narcolepsy is an often misdiagnosed,[12-14] incurable,[7,15] chronic and potentially disabling neurologic disorder,[7-9] and is associated with high medical comorbidity burdens[16] and reduced daily function.[8,11] Narcolepsy has also been shown to have substantial socioeconomic burden[3,6] resulting from increased healthcare resource utilization[1,2] and lower work productivity[2] relative to those without narcolepsy.

For more information about narcolepsy, please contact your Jazz Pharmaceuticals Account Manager.

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