

A Comprehensive Clinical Reference on Common Chronic Illnesses in Primary Care

1. Introduction: The Landscape of Primary Care

Primary care providers (PCPs) serve as the frontline for managing a vast spectrum of health concerns across all age groups and genders. Their responsibilities encompass both acute illnesses, such as colds, influenza, ear infections, and minor injuries, and the crucial, ongoing management of chronic conditions.¹ The breadth of family medicine extends to preventive care, comprehensive chronic disease management, acute illness and injury treatment, mental health support, and specialized care for pediatric, women's, men's, and geriatric populations, alongside dermatological conditions and end-of-life care.³

Common reasons for patient visits to PCPs, as reported by clinicians, frequently include upper respiratory tract infections, hypertension, routine health maintenance, arthritis, diabetes, depression or anxiety, pneumonia, acute otitis media, back pain, and dermatitis.⁴ Among these, chronic conditions like diabetes, high blood pressure, high cholesterol, heart disease, asthma, arthritis, and chronic obstructive pulmonary disease (COPD) are notably prevalent and necessitate sustained clinical attention.² A critical aspect of primary care is the detection of conditions such as cancer, diabetes, and high blood pressure, which often present asymptotically in their early stages, thereby emphasizing the indispensable role of screenings and proactive preventive measures.²

This report is designed to serve as a comprehensive, evidence-based reference for medical doctors. It aims to synthesize current knowledge, diagnostic methodologies, management guidelines, and emerging therapeutic strategies for key chronic illnesses commonly encountered in primary care, thereby supporting informed clinical decision-making.

2. Hypertension

Etiology, Pathophysiology, and Global Epidemiology

Hypertension, commonly known as high blood pressure, represents a pervasive medical condition characterized by persistently elevated force of blood against the artery walls. This sustained pressure compels the heart to exert greater effort to circulate blood throughout the body, a phenomenon measured in millimeters of mercury (mm Hg).⁵ The global burden of hypertension is substantial, affecting over 1 billion individuals worldwide, a figure that continues to escalate.⁶ In 2019 alone, an

estimated 1.28 billion adults aged 30–79 years globally were diagnosed with hypertension.

The development of hypertension is influenced by a complex interplay of modifiable and non-modifiable factors. Modifiable lifestyle elements include diets excessively high in sodium and deficient in potassium, inadequate physical activity, excessive alcohol consumption, tobacco use, chronic stress, insufficient sleep, and the use of certain substances like cocaine or methamphetamines.⁶ The global rise in hypertension prevalence is significantly linked to the adoption of Westernized dietary habits and increasingly sedentary lifestyles.⁶ Non-modifiable factors contributing to risk encompass age, as blood pressure naturally tends to rise with advancing age due to the thickening and stiffening of blood vessels.⁸ A familial predisposition and genetic factors, often polygenic in nature, also play a role, with some individuals exhibiting a heightened sensitivity to dietary salt.⁷ Furthermore, racial and ethnic backgrounds contribute to risk, with Black individuals, for instance, experiencing some of the highest rates of hypertension globally.⁷ Sex-based differences are also observed, with men more susceptible during middle age and women in older adulthood, particularly if they experienced high blood pressure during pregnancy.⁸

Comorbid health conditions significantly increase the risk of developing or exacerbating hypertension. These include elevated blood pressure (often termed pre-hypertension), diabetes (affecting approximately 60% of individuals with diabetes), obesity, which necessitates increased cardiac workload and is associated with dyslipidemia, and pregnancy-induced hypertension.⁵ Chronic kidney disease, metabolic syndrome, sleep apnea, and thyroid disorders are also recognized contributors.⁵ Additionally, certain medications, such as antidepressants, decongestants, hormonal birth control pills, and non-steroidal anti-inflammatory drugs (NSAIDs), can elevate blood pressure.⁵ Beyond individual health, broader social determinants, including income, education level, geographic location, occupation, job-related stressors, experiences of discrimination, and poverty, have been identified as factors that can increase the risk of hypertension.⁸

At a pathophysiological level, sustained elevated blood pressure induces structural alterations within the heart. These changes typically manifest as left ventricular hypertrophy (LVH), an increase in left ventricular muscle mass, or remodeling, characterized by normal mass but increased relative wall thickness.⁹ LVH involves both the enlargement of individual myocardial cells and the development of interstitial fibrosis. These structural adaptations lead to a critical imbalance between the heart's oxygen demand and its supply, frequently resulting in myocardial ischemia, even in the presence of otherwise normal epicardial coronary arteries due to microvascular

dysfunction.⁹ The impaired ventricular compliance and diastolic filling caused by LVH elevate left ventricular end-diastolic pressure (LVEDP) and left atrial pressure. If left unaddressed, this can progress to pulmonary hypertension and significantly increase the risk of atrial fibrillation, further compromising cardiac output and elevating stroke risk.⁹ Moreover, the heart's coronary reserve is diminished due to perivascular fibrosis, narrowing of small arteries, arterial wall stiffening, endothelial dysfunction, and microvascular rarefaction, all contributing to impaired relaxation and characteristic echocardiographic findings.⁹

Clinical Presentation, Diagnostic Criteria, and Staging

Hypertension is often referred to as a "silent killer" because it typically presents without overt symptoms.⁵ However, in severe cases, such as a hypertensive crisis (blood pressure exceeding 180/120 mmHg), patients may experience acute symptoms including chest pain, shortness of breath, back pain, numbness, weakness, changes in vision, or difficulty speaking, necessitating immediate emergency medical attention.⁵ Less specific symptoms like headaches, general shortness of breath, and nosebleeds may also be observed in some individuals.⁵

The diagnostic thresholds and staging of hypertension vary among major international guidelines, which can lead to differences in classification and management approaches. The American Heart Association (AHA) and American College of Cardiology (ACC) 2017 guidelines redefined hypertension as a persistent average systolic blood pressure (SBP) of ≥ 130 mmHg or diastolic blood pressure (DBP) of ≥ 80 mmHg.¹¹ Under these guidelines, normal blood pressure is defined as $<120/80$ mmHg, elevated blood pressure as $120-129/80$ mmHg, Stage 1 hypertension as $130-139/80-89$ mmHg, and Stage 2 hypertension as $\geq 140/90$ mmHg.¹⁰ In contrast, European Society of Hypertension (ESH) and National Institute for Health and Care Excellence (NICE) guidelines generally maintain a clinic blood pressure diagnostic threshold of $\geq 140/90$ mmHg.¹² Their classifications include normal ($<120/80$ mmHg), high-normal (ESH: $120-139/80-89$ mmHg), Grade 1 (ESH)/Stage 1 (NICE) hypertension ($140-159/90-99$ mmHg), Grade 2 (ESH)/Stage 2 (NICE) hypertension ($160-179/100-109$ mmHg), and Grade 3 (ESH)/Stage 3 (NICE) hypertension ($\geq 180/110$ mmHg).¹²

Diagnosis of hypertension requires repeated measurements, both within and outside the clinical setting.¹² Ambulatory Blood Pressure Monitoring (ABPM) is considered the gold standard for diagnosis. This method automatically records blood pressure at regular intervals over a 24- to 48-hour period, capturing the dynamic fluctuations that occur throughout daily life. ABPM is more accurate for diagnosing Stage 1 hypertension than a single office visit and is effective in detecting white coat

hypertension (WCH), where readings are high only in a clinical setting, and masked hypertension (MH), where office readings are normal but out-of-office readings are high.¹¹ Home Blood Pressure Monitoring (HBPM) is also recommended to confirm office readings and identify WCH or MH. Patients should be instructed to take at least two readings, one minute apart, twice daily for 4 to 7 days.¹¹ During office visits, blood pressure should be measured in both arms at initial diagnosis, as a significant difference of greater than 15 mmHg between arms can indicate underlying vascular disease.¹⁵

The diagnostic process also involves ruling out secondary causes of hypertension. Conditions such as fibromuscular dysplasia, atherosclerotic disease, various kidney conditions, thyroid problems, obstructive sleep apnea, and the use of certain medications can contribute to secondary hypertension.⁵ Initial laboratory workup typically includes blood tests to assess levels of potassium, sodium, creatinine, blood glucose, total cholesterol, triglycerides, and thyroid-stimulating hormone (TSH), along with a urinalysis and an electrocardiogram (EKG).¹⁴ Imaging studies, such as renal ultrasound or CT/MRI of the kidneys and adrenal glands, may be necessary if a secondary cause is suspected.¹⁴

Management Strategies

The management of hypertension is multifaceted, encompassing both non-pharmacological and pharmacological approaches. Lifestyle modifications form the cornerstone of both prevention and treatment across all major guidelines.⁶ Dietary changes are paramount, emphasizing reduced sodium intake (ideally no more than 2,400 mg/day) and increased consumption of potassium-rich foods like fruits and vegetables, often guided by the Dietary Approaches to Stop Hypertension (DASH) eating plan.⁷ Weight reduction is a critical component, with the aim of achieving and maintaining a healthy body weight; even a modest loss of 5-7% of current body weight can significantly lower blood pressure.⁸ Regular physical activity, comprising moderate-to-vigorous intensity exercise for at least 3-4 days a week, averaging 40 minutes per session, or a minimum of 150 minutes per week of moderate-intensity activity, is highly recommended.⁷ Moderation of alcohol intake (no more than one drink per day for women and two for men) and complete smoking cessation are essential for reducing cardiovascular risk.⁷ Additionally, stress management and ensuring adequate, good-quality sleep are recognized as important lifestyle interventions.⁸

Pharmacological therapy is initiated based on specific blood pressure thresholds and a patient's overall cardiovascular risk profile, with notable differences across

guidelines. The AHA/ACC guidelines recommend initiating drug therapy for Stage 1 hypertension (130-139/80-89 mmHg) if the patient has established atherosclerotic cardiovascular disease (ASCVD) or a 10-year cardiovascular disease (CVD) risk of $\geq 10\%$. For Stage 2 hypertension ($\geq 140/90$ mmHg), medication is always recommended regardless of risk.¹⁰ Conversely, ESH and NICE guidelines generally advise initiating drug therapy for Grade 1 hypertension (140-159/90-99 mmHg) if the patient is at high risk due to conditions such as hypertension-mediated organ damage (HMOD), diabetes, or chronic kidney disease, or if their 1-year SCORE risk is between 5-10%. Medication is also recommended for all Grade 2 and 3 hypertension.¹² NICE also suggests considering treatment for younger patients (under 60 years) with a QRISK score below 10% based on shared decision-making.¹⁵ The JNC 8 guidelines recommended initiating drug therapy for the general population aged 60 years or older at SBP ≥ 150 mmHg or DBP ≥ 90 mmHg. For individuals younger than 60, the target DBP to start therapy is ≥ 90 mmHg (Grade A recommendation), and SBP ≥ 140 mmHg (Grade E recommendation). For patients with chronic kidney disease or diabetes, JNC 8 suggested initiating treatment at SBP ≥ 140 mmHg or DBP ≥ 90 mmHg.¹⁸

Blood pressure targets also vary by guideline. The AHA/ACC generally aims for a target of $<130/80$ mmHg for most patients, with a systolic target of <130 mmHg for those aged 65 years or older.¹² The ESH guidelines propose an initial target of $<140/90$ mmHg, with an ultimate goal of $<130/80$ mmHg. They provide age-specific targets: 120-129/ <80 mmHg for those under 65 years, 130-139/ <80 mmHg (if tolerated) for ages 65-79 years, and 130-139/ <80 mmHg for those over 80 years.¹² Notably, for patients with chronic kidney disease, ESH recommends a target of $<140/90$ mmHg, which differs from the AHA/ACC's $<130/80$ mmHg.¹³ NICE guidelines advise a clinic BP target of $<140/90$ mmHg or $<135/85$ mmHg (if using HBPM) for patients under 80 years. For those over 80 years with Stage 2 hypertension, the target is $\leq 150/90$ mmHg.¹⁵

The initial choice of antihypertensive agents typically involves one of four major classes: Angiotensin-converting enzyme inhibitors (ACEI), Angiotensin receptor blockers (ARB), Thiazide-type diuretics, or Calcium channel blockers (CCB).¹² JNC 8 specifically recommended that for non-Black patients (including those with diabetes), initial therapy should include a thiazide-type diuretic, CCB, ACEI, or ARB. For Black patients (including those with diabetes), a thiazide-type diuretic or CCB is recommended. In patients with chronic kidney disease, an ACEI or ARB is indicated regardless of race or diabetic status.²² NICE guidelines suggest ACEI, ARB, or CCB as first-line, with a diuretic as an alternative if CCB is not tolerated or if the patient has

edema or heart failure. ACEI or ARB are preferred for patients under 55 years.¹⁶

Combination therapy is often necessary to achieve blood pressure goals. The AHA/ACC guidelines recommend an initial two-drug regimen for Stage 2 hypertension when blood pressure is >20/10 mmHg above target, and specifically for Black patients.¹³ ESH guidelines advocate for initial therapy with a two-drug combination for most patients.¹³ JNC 8 also suggests starting with two drugs if the blood pressure is >20/10 mmHg above goal.¹⁸ A stepwise approach involves increasing the dose of the initial drug, then adding a second, and subsequently a third if goals are not met.¹⁵ It is crucial to note that ACEI and ARB should not be combined in the same patient.²² For resistant hypertension, defined as uncontrolled blood pressure despite optimal doses of three antihypertensive agents (including a diuretic), consideration should be given to adding low-dose spironolactone (if potassium levels are ≤4.5 mmol/l), an alpha-blocker, or a beta-blocker, along with referral to a hypertension specialist.¹⁵ Specific indications for drug choices include heart failure (ACEI/ARB + beta-blocker + diuretic + spironolactone), post-myocardial infarction/clinical coronary artery disease (ACEI/ARB and beta-blocker), diabetes (ACEI/ARB, CCB, diuretic), chronic kidney disease (ACEI/ARB), recurrent stroke prevention (ACEI, diuretic), and pregnancy (labetalol, nifedipine, methyldopa).¹⁸

Table 1: Comparison of Hypertension Diagnostic and Treatment Thresholds (AHA/ACC vs. ESH/NICE)

Characteristic	AHA/ACC (2017)	ESH (2023)	NICE (UK)
Normal BP Definition	<120/80 mmHg	<120/80 mmHg	<140/90 mmHg (Clinic)
Elevated/High-Normal BP	Elevated: 120-129/<80 mmHg	High-Normal: 120-139/80-89 mmHg	N/A
Stage/Grade 1 HTN	Stage 1: 130-139/80-89 mmHg	Grade 1: 140-159/90-99 mmHg	Stage 1: Clinic ≥140/90 mmHg AND ABPM/HBPM ≥135/85 mmHg
Stage/Grade 2 HTN	Stage 2: ≥140/90 mmHg	Grade 2: 160-179/100-109 mmHg	Stage 2: Clinic ≥160/100 mmHg AND ABPM/HBPM ≥150/95

			mmHg
Stage/Grade 3 HTN	N/A	Grade 3: $\geq 180/110$ mmHg	Stage 3 (Severe): Clinic $\geq 180/120$ mmHg (no ABPM/ HBPM needed)
Primary Diagnostic Method	Office BP, confirmed by ABPM/ HBPM	Office BP, confirmed by ABPM/ HBPM	ABPM (gold standard), HBPM alternative
Threshold for Pharmacological Treatment Initiation (General Population)	Stage 1 if ASCVD or 10-yr CVD risk $\geq 10\%$; Always for Stage 2	Grade 1 if high risk (e.g., HMOD, DM, CKD, SCORE 5-10%); Always for Grade 2/3	Stage 1 if 10-yr CVD risk $\geq 10\%$ OR target organ damage/CVD/renal disease/DM; Always for Stage 2/3
BP Target for Most Patients	$<130/80$ mmHg	Initial: $<140/90$ mmHg; Ultimate: $<130/80$ mmHg	Clinic $<140/90$ mmHg OR HBPM $<135/85$ mmHg
BP Target for Specific Populations (e.g., elderly, CKD)	≥ 65 yrs: SBP <130 mmHg	65-79 yrs: $130-139/<80$ mmHg (if tolerated); >80 yrs: $130-139/<80$ mmHg; CKD: $<140/90$ mmHg	>80 yrs (Stage 2): $\leq 150/90$ mmHg
Key Non-Pharmacological Recommendations	DASH diet, sodium restriction, weight loss, physical activity, alcohol moderation, smoking cessation, stress management, adequate sleep	DASH diet, sodium restriction, weight reduction, physical activity, alcohol moderation	Diet, exercise, sodium restriction, alcohol moderation, weight reduction

Complications, Prognosis, and Prevention

Uncontrolled hypertension poses a significant threat to long-term health, as the persistent, excessive pressure on arterial walls leads to progressive damage of blood vessels and vital organs.⁵ This damage underpins a range of severe complications. Cardiovascular complications are particularly prominent, including heart attack, various forms of heart disease (coronary artery disease, congestive heart failure, left

ventricular hypertrophy), stroke, aortic dissection, atherosclerosis, aneurysm formation, and angina.⁵ Hypertension is recognized as the single largest contributor to cardiovascular disease and remains the leading risk factor for cardiovascular death globally.⁶ Beyond the cardiovascular system, uncontrolled hypertension can lead to significant kidney damage, progressing to chronic kidney disease.⁵ Ocular complications can result in vision loss due to thickened, narrowed, or torn blood vessels in the eyes.⁵ Neurological and cognitive impairments, such as memory loss, alterations in thinking and understanding, and vascular dementia, are also potential consequences, often stemming from stroke or chronic cerebral hypoperfusion.⁵ Other complications include erectile dysfunction, fluid accumulation in the lungs, and the development of metabolic syndrome, a cluster of conditions including increased waist size, high triglycerides, low HDL cholesterol, high blood pressure, and elevated blood sugar.⁵

The prognosis for individuals with hypertension is directly correlated with the severity and duration of uncontrolled blood pressure; the higher the blood pressure and the longer it remains unmanaged, the greater the extent of organ damage and the risk of developing these severe complications.⁵ Therefore, early detection and diligent management are paramount to improving long-term outcomes. Prevention of hypertension primarily relies on the adoption and maintenance of healthy lifestyle habits throughout life.⁷ Regular routine check-ups and screenings are vital for identifying elevated blood pressure early, allowing for timely intervention before it progresses to established hypertension or causes irreversible organ damage.²

Recent Advancements and Emerging Therapies

Despite established management strategies, resistant hypertension—defined as persistently elevated blood pressure despite adherence to multiple antihypertensive therapies—remains a significant global health challenge. This condition is associated with heightened cardiovascular morbidity and mortality, underscoring the urgent need for more effective treatment strategies.²⁴ Recent advancements in therapeutic approaches for hypertension are increasingly targeting novel mechanisms, including gene silencing, receptor modulation, enzyme inhibition, and immunomodulation.²⁴

A particularly promising area of development is the investigation of aldosterone synthase inhibitors, such as lorundrostat. This investigational oral drug shows significant promise for patients with uncontrolled or treatment-resistant hypertension.²⁵ The importance of this therapeutic avenue stems from the recognition that abnormally elevated aldosterone levels are an often underrecognized cause of treatment-resistant hypertension.²⁵ A Phase 2b trial (Advance-HTN) demonstrated

that lorundrostat led to a significant reduction in 24-hour systolic blood pressure, showing a 15.4-point drop for the 50mg dose and a 13.9-point drop for the 50-100mg dose, compared to a 7.4-point reduction in the placebo group.²⁵ The effectiveness of lorundrostat was observed irrespective of race, gender, or weight, which is particularly relevant given the disproportionately high prevalence of hypertension among Black Americans.²⁶ While these results are encouraging, higher rates of hyperkalemia and hyponatremia were noted at higher doses.²⁷ To further validate these findings, larger Phase 3 trials are currently underway.²⁵

The redefinition of hypertension by the AHA/ACC guidelines to a lower threshold of 130/80 mmHg, compared to the traditional 140/90 mmHg, represents a substantial shift in clinical perspective. This change was driven by compelling data indicating an approximately twofold increase in cardiovascular events and mortality in adults with blood pressure in the 130-139/80-89 mmHg range compared to those with normal blood pressure.¹¹ This revised definition significantly expands the population classified as hypertensive, particularly in the United States, where prevalence estimates increased from 31.9% to 45.6% following the adoption of these new guidelines.⁶ This reclassification presents a considerable public health challenge, necessitating more widespread lifestyle interventions and potentially earlier pharmacological treatment for a larger segment of the population. It underscores the critical need for clinicians to be aware of the specific guidelines being referenced when diagnosing and managing hypertension. The emphasis on out-of-office blood pressure measurements, such as ABPM and HBPM, becomes even more crucial in this context to prevent over-diagnosis or misdiagnosis based solely on clinic readings, especially with the lower diagnostic thresholds.¹¹ This expansion of the hypertensive population also implies a potential for increased healthcare burden and costs associated with a greater number of diagnoses and treatments, highlighting a societal ripple effect that warrants careful consideration.

The focus on aldosterone as an underrecognized contributor to treatment-resistant hypertension, as highlighted by the development and trial results of lorundrostat, signifies a move towards more targeted therapeutic approaches. This suggests that for patients whose blood pressure remains uncontrolled despite conventional multi-drug regimens, a deeper investigation into the renin-angiotensin-aldosterone system (RAAS) and aldosterone levels may be clinically beneficial. The emergence of aldosterone synthase inhibitors as a novel drug class indicates a strategic shift in pharmacological development, aiming to address specific pathophysiological mechanisms rather than relying solely on broad-spectrum antihypertensives. This development holds the promise of more personalized and potentially more effective

treatment strategies for individuals with challenging hypertension, moving beyond the traditional empiric approach to resistant cases.

3. Type 2 Diabetes Mellitus (T2DM)

Etiology, Pathophysiology, and Global Epidemiology

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder fundamentally characterized by persistently elevated blood glucose levels. This hyperglycemia arises from a combination of two primary defects: insufficient insulin secretion by the pancreatic β -cells and/or a diminished ability of insulin-sensitive tissues to respond appropriately to insulin, a phenomenon known as insulin resistance.²⁸ Over time, chronic high blood sugar levels inflict widespread damage across various organ systems, including the heart, vasculature, eyes, kidneys, and nerves.²⁸

The global prevalence of T2DM is alarmingly high and continues to rise. In the United States, over 38 million individuals live with diabetes, with T2DM accounting for 90-95% of these cases.²⁹ Globally, in 2021, an estimated 529 million people were living with diabetes, a figure projected to surge to 1.31 billion by 2050.³³ T2DM constitutes the vast majority of diabetes cases worldwide, representing 96% of all diagnoses.³³ A concerning trend is the increasing incidence of T2DM among younger populations, including children, teenagers, and young adults.²⁹

Numerous risk factors contribute to the development of T2DM. Modifiable lifestyle factors are paramount, with overweight and obesity, particularly the accumulation of abdominal fat, being the primary risk factors.¹⁹ Physical inactivity and unhealthy dietary patterns further exacerbate this risk.¹⁹ High body mass index (BMI) alone was responsible for a substantial 52.2% of global T2DM disability-adjusted life-years (DALYs) in 2021.³³ Additionally, chronic stress and inadequate sleep quality are recognized as contributing factors.³¹ Non-modifiable risk factors include age, with the risk of T2DM increasing significantly after 35 years and being most common in individuals aged 45 or older.¹⁹ A strong family history also plays a role, with a 40% lifetime risk if one biological parent has T2DM and a 70% risk if both parents are affected.³¹ Certain racial and ethnic groups, including African American, Hispanic/Latino, American Indian, Alaska Native, and some Pacific Islander and Asian American populations, exhibit a higher predisposition to the disease.¹⁹

Several comorbid conditions and predisposing factors also elevate the risk of T2DM. These include prediabetes, a precursor state where blood sugar levels are elevated but not yet diagnostic of diabetes, and a history of gestational diabetes during pregnancy or giving birth to a baby weighing over 9 pounds.¹⁹ Polycystic ovary

syndrome (PCOS), non-alcoholic fatty liver disease (NAFLD), high blood pressure, high cholesterol, and certain hormonal disorders such as hypothyroidism and Cushing syndrome are also associated with increased T2DM risk.¹⁹

The pathophysiology of T2DM is complex and involves a progressive decline in glucose regulation. The central mechanism is insulin resistance, where cells in muscles, fat, and the liver fail to respond normally to insulin, thereby impeding adequate glucose uptake.²⁹ Initially, the pancreas attempts to compensate for this resistance by producing excessive amounts of insulin (hyperinsulinemia). However, over time, the pancreatic beta-cells become exhausted and damaged, losing their capacity to produce sufficient insulin to maintain glucose homeostasis, ultimately leading to chronic hyperglycemia.²⁹ Emerging research also points to the involvement of other factors in T2DM pathogenesis, including adipokine dysregulation, systemic inflammation, and alterations in gut microbiota and immune function.²⁸ A critical concept in T2DM is "metabolic memory," which refers to the persistence and progression of diabetic complications even after blood glucose levels are brought under control.²⁸ This phenomenon is attributed to permanent abnormalities in target organs and cells, such as aberrant gene expression, induced by the initial period of hyperglycemia. Metabolic memory is thought to involve mechanisms such as epigenetics, oxidative stress, non-enzymatic glycation of proteins, and chronic inflammation.²⁸

Clinical Presentation, Diagnostic Criteria, and Screening

The clinical presentation of Type 2 Diabetes Mellitus (T2DM) often develops insidiously over several years, with symptoms that may initially be subtle or go unnoticed.²⁹ Common symptoms, when they do appear, include increased thirst (polydipsia) and frequent urination (polyuria), increased hunger (polyphagia) despite adequate food intake, persistent fatigue, blurred vision, slow-healing cuts or bruises, and sensations of tingling, pain, or numbness in the hands and feet, indicative of neuropathy.¹⁹ Unexplained weight loss can also occur. In women, recurrent vaginal yeast infections and/or urinary tract infections (UTIs) may be presenting complaints.³¹

The diagnosis of T2DM is definitively established through blood tests, requiring two abnormal test results from the same sample or from two different samples.³⁷ Key diagnostic criteria, as outlined by organizations such as the American Diabetes Association (ADA), World Health Organization (WHO), and American Association of Clinical Endocrinologists (AACE), include:

- **A1C Test:** This test measures the average blood sugar level over the preceding 2-3 months.

- Normal: Below 5.7% ³⁶
- Prediabetes: 5.7% to 6.4% ³⁶
- Diabetes: 6.5% or higher (confirmed by a second test) ³⁶
- **Fasting Plasma Glucose (FPG) Test:** This test requires an 8-hour fast prior to blood collection.
 - Normal: Less than 100 mg/dL (5.6 mmol/L) ³⁶
 - Prediabetes: 100 to 125 mg/dL (5.6 to 6.9 mmol/L) ³⁶
 - Diabetes: 126 mg/dL (7 mmol/L) or higher (confirmed by a second test) ³⁶
- **Oral Glucose Tolerance Test (OGTT):** This test measures blood sugar levels before and 2 hours after consuming a sugary liquid.
 - Normal: Less than 140 mg/dL (7.8 mmol/L) after 2 hours ³⁶
 - Prediabetes: 140 to 199 mg/dL (7.8 to 11.0 mmol/L) after 2 hours ³⁶
 - Diabetes: 200 mg/dL (11.1 mmol/L) or higher after 2 hours ³⁶
- **Random Plasma Glucose (RPG) Test:** This test can be performed at any time, without prior fasting.
 - Diabetes: 200 mg/dL (11.1 mmol/L) or higher, in conjunction with symptoms of hyperglycemia ³⁶

Table 2: Diagnostic Criteria for Type 2 Diabetes Mellitus

Test Type	Normal Range	Prediabetes Range	Diabetes Range	Preparation Required	Notes
A1C Test	<5.7%	5.7% - 6.4%	≥6.5%	None	Average blood sugar over 2-3 months; diagnosis requires two separate tests for confirmation.
Fasting Plasma Glucose (FPG) Test	<100 mg/dL (<5.6 mmol/L)	100-125 mg/dL (5.6-6.9 mmol/L)	≥126 mg/dL (≥7 mmol/L)	8-hour fast	Diagnosis requires two separate tests for confirmation.
Oral	<140 mg/dL	140-199	≥200 mg/dL	8-hour fast,	Diagnosis

Glucose Tolerance Test (OGTT)	(<7.8 mmol/L) (2-hr post-glucose)	mg/dL (7.8-11.0 mmol/L) (2-hr post-glucose)	(≥11.1 mmol/L) (2-hr post-glucose)	then consume sugary liquid	requires two separate tests for confirmation.
Random Plasma Glucose (RPG) Test	N/A	N/A	≥200 mg/dL (≥11.1 mmol/L)	None	Used with symptoms of hyperglycemia; single test can be diagnostic if symptoms are present.

Routine screening for T2DM is recommended for individuals with identified risk factors.³⁸ The AACE guidelines suggest periodic screening after the age of 35 years, with earlier screening considered for high-risk ethnic groups.⁴⁰ All pregnant women should undergo screening for T2DM at their first prenatal appointment and for gestational diabetes between 24 and 28 weeks of pregnancy.³⁸ While symptoms can overlap with other conditions, blood tests provide definitive diagnosis.³⁷

Management Strategies

The management of Type 2 Diabetes Mellitus (T2DM) necessitates a comprehensive, person-centered approach that integrates multifactorial behavioral and pharmacological treatments. The overarching goals are to prevent or delay complications and maintain the patient's quality of life, with a strong emphasis on patient engagement in self-care activities.⁴⁰

Lifestyle modifications are fundamental to diabetes care and form the bedrock of any treatment plan.¹⁹ Medical Nutrition Therapy (MNT) involves adopting healthy eating patterns, focusing on balanced diets with smaller portions, limiting caloric intake (especially if overweight), reducing fat consumption, and substituting sweetened beverages with water.¹⁹ Regular physical activity is crucial, with a recommendation of at least 150 minutes per week of moderate-to-vigorous aerobic activity, coupled with efforts to reduce sedentary time.¹⁹ Weight management is a key component, as losing even 5-7% of current body weight can significantly prevent or delay T2DM progression.¹⁹ Beyond diet and exercise, psychological support, including counseling on healthy lifestyle habits, stress management techniques, and addressing tobacco or

substance abuse, is an integral part of holistic care.²⁹

Pharmacological therapy often complements lifestyle interventions. Metformin is the preferred initial pharmacologic agent for most patients at the time of diagnosis, holding a Grade A recommendation.⁴² The expanding array of glucose-lowering interventions now includes various pharmacological agents, as well as devices and surgical options.⁴¹ A significant advancement in T2DM management is the recognition of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT2i). These agents have demonstrated substantial benefits for high-risk individuals with atherosclerotic cardiovascular disease (ASCVD), heart failure, or chronic kidney disease, largely independent of their glucose-lowering effects.⁴¹ Consequently, these medications are now prescribed not only for glucose control but also for their organ-protective properties.⁴¹

Insulin therapy may become necessary if lifestyle modifications and other oral medications are insufficient to achieve glycemic targets.¹⁹ Basal insulin is often the most convenient initial insulin therapy, with starting doses estimated based on body weight (0.1-0.2 IU/kg per day) or a standard 10-IU daily dose, subsequently titrated based on self-monitored blood glucose levels.⁴² Long-acting insulin analogues such as detemir or glargine have shown reduced hypoglycemia risk compared to human neutral protamine Hagedorn (NPH) insulin.⁴² Prandial insulin may be added to manage postprandial glucose excursions, typically starting with 4 IU or 10% of the basal insulin dose before the largest meal.⁴² The cost of insulin is a critical factor influencing patient adherence, and clinicians should be aware of more affordable human insulin options (regular and NPH).⁴²

The American Association of Clinical Endocrinologists (AACE) provides specific glycemic targets. For most patients without serious illness and at low hypoglycemic risk, an HbA1c target of $\leq 6.5\%$ is recommended, with preprandial plasma glucose < 110 mg/dL and postprandial plasma glucose < 140 mg/dL.³⁹ A less stringent HbA1c goal of 7-8% is advised for patients with a history of severe hypoglycemia, hypoglycemia unawareness, short life expectancy, advanced renal failure, multiple concomitant illnesses, or long-standing diabetes that has been difficult to control.³⁹ AACE guidelines also outline a stepwise approach to treatment escalation. If a patient is not at glycemic target after 3 months of monotherapy (A1C $> 6.5\%$) or presents with an initial A1C $> 7.5\%$, dual therapy is recommended. For individuals with an initial A1C $> 9\%$ or 1.5% above goal, dual or triple therapy should be initiated concomitantly.³⁹ In cases of symptomatic hyperglycemia, an A1C $> 10\%$, and/or basal glucose > 300 mg/dL, insulin therapy should be considered, either initially or as an addition to dual or triple

therapy.³⁹

Table 3: Key Pharmacological Agents for Type 2 Diabetes Mellitus

Drug Class	Primary Mechanism of Action	Key Benefits	Key Side Effects/Considerations	Typical Use/Indications
Metformin	Decreases hepatic glucose production, improves insulin sensitivity	First-line, weight-neutral, low hypoglycemia risk, inexpensive	GI upset (nausea, diarrhea), lactic acidosis (rare)	First-line for most patients, especially with overweight/obesity
Sulfonylureas (SFU)	Stimulate insulin secretion from beta-cells (glucose-independent)	Rapid glucose lowering, inexpensive	Hypoglycemia, weight gain	Second-line, often used with metformin, caution in elderly/renal impairment
Thiazolidinediones (TZD)	Improve insulin sensitivity in peripheral tissues (muscle, fat)	Durable glycemic control, low hypoglycemia risk	Weight gain, fluid retention, heart failure, bone fractures	Second-line, caution in heart failure
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors	Enhance incretin effect by preventing GLP-1/GIP breakdown	Weight-neutral, low hypoglycemia risk, oral	Joint pain, rare pancreatitis, no renal adjustment for some (linagliptin)	Add-on therapy, especially for patients needing modest HbA1c reduction
Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs)	Mimic incretin hormones: glucose-dependent insulin secretion, suppress glucagon, slow gastric emptying,	Weight loss, low hypoglycemia risk, CV/renal protection (for some agents), injectable (some oral)	Nausea, vomiting, diarrhea, pancreatitis (rare), thyroid C-cell tumors (rodents)	Add-on, especially for patients with ASCVD, HF, CKD, or obesity

	promote satiety			
Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors	Increase urinary glucose excretion by inhibiting renal reabsorption	Weight loss, low hypoglycemia risk, CV/renal protection	Genital mycotic infections, UTIs, dehydration, hypotension, DKA (euglycemic)	Add-on, especially for patients with ASCVD, HF, CKD
Insulin	Replaces endogenous insulin, promotes glucose uptake by cells	Most potent glucose lowering, essential for severe deficiency	Hypoglycemia, weight gain, injection site reactions	Used when oral agents are insufficient, for severe hyperglycemia, or specific clinical situations

Complications, Prognosis, and Prevention

Uncontrolled Type 2 Diabetes Mellitus (T2DM) leads to chronic hyperglycemia, which progressively damages various organ systems throughout the body.³¹ This sustained damage gives rise to a wide array of severe and debilitating complications.

Cardiovascular disease (CVD) is the leading cause of mortality in individuals with diabetes, encompassing conditions such as coronary artery disease (CAD), peripheral artery disease (PAD), cerebrovascular disease, myocardial infarction, and stroke.³¹

Beyond macrovascular complications, T2DM is a primary driver of microvascular damage. Kidney disease, or diabetic nephropathy, is the leading cause of chronic kidney disease (CKD).³¹ Diabetic retinopathy, an eye disease, is the leading cause of new cases of blindness among working-age adults.²⁹ Nerve damage, or neuropathy, affects approximately half of all individuals with diabetes, manifesting as numbness, tingling, or pain, particularly in the extremities.³⁵ These microvascular complications contribute to other significant issues, such as foot problems, which, due to nerve damage and reduced circulation, can lead to severe infections and even limb loss.⁴³ Oral complications, including an increased risk for gingivitis and periodontitis, are also common.⁴³ Furthermore, hearing loss is twice as prevalent in people with diabetes compared to those without the condition.⁴³

Acute complications of T2DM, though less common with modern management, can be life-threatening. These include diabetic ketoacidosis (DKA), a severe condition caused

by an overload of ketones when the body breaks down fat for energy, and hyperosmolar hyperglycemic state (HHS), characterized by extremely high blood sugar levels and significant mental status changes.³¹ T2DM is also associated with other systemic health problems, such as non-alcoholic fatty liver disease (NAFLD), sleep apnea, depression, certain types of cancer, and dementia.¹⁹

The prognosis for individuals with T2DM is highly dependent on several factors: the age at diagnosis, the consistency and effectiveness of blood sugar control, the presence and management of co-existing conditions like hypertension and hyperlipidemia, and access to quality healthcare.³¹ Early and consistent glycemic control has been shown to yield substantial and enduring reductions in the onset and progression of microvascular complications.⁴¹ The concept of "metabolic memory," where initial periods of hyperglycemia can lead to persistent complications even after glucose levels are normalized, underscores the critical importance of early intervention.²⁸

Prevention of T2DM is largely achievable through lifestyle changes. Weight loss, regular physical activity, and adopting a healthy diet can significantly prevent or delay the onset of the disease, particularly in individuals with prediabetes.¹⁹

Recent Advancements and Emerging Therapies

The landscape of Type 2 Diabetes Mellitus (T2DM) treatment is continuously evolving, with significant advancements in pharmacological and non-pharmacological therapies.

Glucagon-Like Peptide 1 Receptor Agonists (GLP-1 RAs), including agents like exenatide, liraglutide, taspoglutide, albiglutide, and lixisenatide, have revolutionized diabetes management. These medications offer several advantages over older therapies: they minimize the risk of hypoglycemia by acting in a glucose-dependent manner, and they promote weight loss by slowing gastric emptying and enhancing satiety.⁴⁴ GLP-1 RAs have demonstrated sustained reductions in HbA1c and improvements in cardiometabolic risk markers, including systolic blood pressure, total cholesterol, and triglyceride levels.⁴⁵ A critical development is their recognized benefit for high-risk individuals with atherosclerotic cardiovascular disease (ASCVD), heart failure, or chronic kidney disease, with these benefits often being independent of their glucose-lowering effects.⁴¹ Newer, longer-acting formulations offer the convenience of once-weekly administration, improving patient adherence.⁴⁴

Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i), such as dapagliflozin, canagliflozin, remogliflozin, etabonate, and sergliflozin, represent another

transformative class of drugs. Their mechanism involves enhancing urinary glucose excretion, thereby lowering blood glucose levels independently of insulin.⁴⁴ SGLT2i have shown efficacy in reducing HbA1c and promoting weight loss, with a lower risk of hypoglycemia compared to sulfonylureas.⁴⁵ Similar to GLP-1 RAs, SGLT2i have demonstrated significant benefits for high-risk patients with ASCVD, heart failure, or chronic kidney disease.⁴¹ Common side effects include an increased incidence of genital and urinary tract infections.⁴⁵

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors, such as linagliptin and alogliptin, are a more recently approved class. Linagliptin is notable for not requiring renal dose adjustments, making it a suitable option for patients with kidney impairment.⁴⁵

Beyond these established classes, several **novel oral anti-diabetic drugs** are in various stages of clinical development:

- **Imeglimin**, a first-in-class "Glimin" drug, acts as an oxidative phosphorylation inhibitor, targeting three key defects of T2DM: insufficient insulin production, excessive hepatic gluconeogenesis, and impaired glucose uptake by skeletal muscles. It is currently in Phase IIa clinical trials.⁴⁴
- **Fructose 1,6-bisphosphatase inhibitors** are being explored for their potential to reduce excessive gluconeogenesis, though current data are primarily from rodent studies.⁴⁴
- **Peroxisome Proliferator-Activated Receptor (PPAR) α/γ ligands**, like aleglitazar, have shown promise in reducing HbA1c and improving lipid profiles, although some agents in this class have raised concerns regarding cardiovascular events.⁴⁴
- **G-protein coupled receptor 119 (GPR119) agonists**, such as MBX-2982, stimulate glucose-dependent incretin and insulin secretion and are in Phase II clinical trials.⁴⁴

Broader research efforts are also focused on understanding the biological mechanisms regulating body weight, developing non-enzymatic continuous glucose monitoring systems, investigating the "legacy effect" of early glucose control on long-term outcomes, exploring immunotherapy to prevent immune-mediated beta-cell destruction, identifying the role of molecules like ceramides in insulin resistance, and assessing the impact of environmental chemicals (e.g., Bisphenol A - BPA) on glucose and insulin levels.⁴⁶ Research is also underway to find new molecules for treating diabetic neuropathy.⁴⁶

The demonstrated benefits of newer diabetes medications, specifically GLP-1 RAs and SGLT2i, extend significantly beyond mere glucose lowering. These agents, initially

developed for glycemic control, are now recognized and prescribed for their profound organ-protective effects, particularly in reducing cardiovascular and renal complications in high-risk individuals.⁴¹ This represents a fundamental shift in the approach to T2DM management. Clinical decision-making is increasingly moving beyond a singular focus on HbA1c targets to a more holistic assessment of a patient's overall cardiovascular and renal risk profile. This prioritization of cardiorenal protection implies that for many high-risk patients, these newer drug classes should be considered early in the treatment algorithm, even if their glucose levels are only moderately elevated. This evolution in understanding underscores the intricate interconnectedness of metabolic, cardiovascular, and renal health, necessitating a comprehensive and integrated treatment strategy.

The concept of "metabolic memory" highlights a critical aspect of T2DM progression. This phenomenon describes how the detrimental effects of initial hyperglycemia can persist and contribute to long-term diabetic complications, even after blood glucose levels are subsequently brought under control.²⁸ This suggests that the early period of uncontrolled blood sugar can induce permanent abnormalities in target organs, such as aberrant gene expression, which continue to drive disease progression regardless of later glycemic improvements.²⁸ This understanding emphasizes the paramount importance of early diagnosis and aggressive, proactive management of T2DM. Delaying optimal glycemic control, even for a relatively short period, may have irreversible consequences on organ health. For clinicians, this reinforces the imperative to screen for T2DM and prediabetes diligently, and to initiate effective therapeutic interventions, encompassing both lifestyle modifications and appropriate pharmacotherapy, as promptly as possible. This approach aims to mitigate the long-term burden of complications by addressing the disease at its earliest stages.

4. Hyperlipidemia

Etiology, Pathophysiology, and Global Epidemiology

Hyperlipidemia, also known as dyslipidemia, is a prevalent metabolic disorder characterized by abnormally elevated levels of lipids and lipoproteins in the bloodstream. This includes high total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides, often accompanied by reduced levels of high-density lipoprotein cholesterol (HDL-C).⁴⁷

The global burden of hyperlipidemia is substantial and growing. Over 3 million adults in the United States and Europe are diagnosed with hyperlipidemia, and this number continues to increase rapidly.⁴⁷ In 2008, the global prevalence of raised total cholesterol among adults was estimated at 39%.⁵⁰ Familial hypercholesterolemia (FH),

a common autosomal-dominant genetic disorder, affects approximately 30 million individuals worldwide, with a general population prevalence estimated at 0.32% (1 in 313 people).⁵¹

The etiology of hyperlipidemia is multifactorial, involving both modifiable lifestyle factors and non-modifiable genetic predispositions. Key modifiable factors include an unhealthy diet rich in saturated and trans fats and high in cholesterol, insufficient physical activity, overweight and obesity (particularly abdominal obesity), smoking, and excessive alcohol consumption.⁴⁷ Non-modifiable factors encompass genetics, with FH being a clear example, and a polygenic inheritance pattern common in most patients.⁴⁷ Age is also a factor, as the liver's ability to clear LDL-C diminishes after age 40.⁵²

Hyperlipidemia can also be secondary to various comorbid conditions. These include uncontrolled diabetes, chronic kidney disease, nephrotic syndrome, hypothyroidism, HIV/AIDS, lupus, obstructive sleep apnea, and cholestatic liver disease.⁴⁷ Certain medications, such as those used for acne, cancer, high blood pressure, HIV/AIDS, irregular heartbeats, and organ transplants, can also adversely affect cholesterol levels.⁵² Chronic inflammatory disorders, including rheumatoid arthritis, psoriasis, and Crohn's disease, are recognized as risk-enhancing factors.⁵⁴

From a pathophysiological perspective, hyperlipidemia, particularly elevated LDL-C, is a primary driver of atherosclerosis and subsequent vascular disease.⁴⁷ Atherosclerosis is a progressive process initiated by endothelial damage, followed by inflammation and the accumulation of lipids within the innermost layer of the arterial wall.⁴⁷ Macrophages engulf these lipids, transforming into "foam cells," which contribute to cholesterol buildup, mitochondrial dysfunction, apoptosis, and ultimately necrosis of the underlying tissues.⁴⁷ This process leads to the formation of atherosclerotic plaques, which can narrow or block arteries. If a plaque ruptures, a blood clot can form, further obstructing blood flow.⁵² LDL-C is the predominant atherogenic cholesterol, while very low-density lipoprotein cholesterol (VLDL-C) also contributes to atherogenesis. Non-HDL-C (the sum of LDL-C and VLDL-C) and apolipoprotein B (apoB), the main protein embedded in LDL and VLDL, are considered stronger indicators of atherogenicity than LDL-C alone.⁵⁴

Clinical Presentation, Diagnostic Criteria, and Risk Assessment

Hyperlipidemia is typically asymptomatic until significant atherosclerosis has developed, making it a silent risk factor for cardiovascular disease.⁴⁸ However, in cases of very high cholesterol, particularly familial forms, certain physical signs may be present. These include xanthomas (fatty deposits under the skin), xanthelasmas (fatty

deposits around the eyes), tendinous xanthomas (fatty deposits in tendons), and arcus cornealis (a white or gray ring around the cornea) appearing before the age of 45.⁴⁸

Diagnosis of hyperlipidemia is primarily made through a lipid profile, also known as a lipid panel or lipoprotein panel.⁴⁸ This blood test measures total cholesterol, LDL-C, HDL-C, and triglycerides.⁴⁸ Non-HDL-C, calculated as total cholesterol minus HDL-C, is also an important parameter.⁴⁸ Patients are often asked to fast for 8-12 hours before a lipid panel, especially if initial non-fasting triglyceride levels are ≥ 400 mg/dL.⁵⁷

Routine screening frequency for hyperlipidemia varies by age and risk factors:

- **Ages 19 or younger:** Screening typically begins between ages 9 and 11 and should be repeated every 5 years. Earlier screening, as early as age 2, is recommended if there is a family history of high cholesterol or cardiovascular disease.⁵⁷
- **Ages 20 to 65:** Younger adults should be screened every 5 years. For men aged 45-65 and women aged 55-65, screening is advised every 1-2 years.⁵⁷
- **Older than 65:** Annual screening is recommended.⁵⁷

A lipoprotein(a) [Lp(a)] test is not part of a routine lipid panel but may be ordered if there is a family history of early cardiovascular disease or stroke, as high Lp(a) levels indicate increased CVD risk even with otherwise healthy cholesterol levels.⁵⁵

Risk assessment is crucial for guiding management decisions. The Atherosclerotic Cardiovascular Disease (ASCVD) Risk Calculator, recommended by the AHA/ACC for adults aged 40-75 years without established ASCVD, helps estimate the 10-year risk of cardiovascular events.²⁰ The presence of additional risk-enhancing factors, such as a family history of premature ASCVD, persistently elevated LDL-C ≥ 160 mg/dL, metabolic syndrome, chronic kidney disease, a history of preeclampsia or premature menopause before age 40, or chronic inflammatory disorders, further refines this risk assessment.⁵⁴ Coronary artery calcium (CAC) scanning can also provide additional information to guide preventive interventions.²⁰

Management Strategies

The management of hyperlipidemia is founded upon a dual approach of non-pharmacological interventions and, when necessary, pharmacological therapy. Lifestyle modifications are considered foundational therapy for atherosclerotic cardiovascular disease (ASCVD) risk reduction across all age groups.²⁰ Dietary changes are paramount, emphasizing increased intake of vegetables, fruits, legumes,

nuts, whole grains, lean protein, and fish, while simultaneously reducing total fat intake to 30% or less of total energy, saturated fats to 7% or less, and completely eliminating trans fats.²⁰ Replacing saturated fats with monounsaturated and polyunsaturated fats (e.g., olive oil, rapeseed oil, fatty fish, nuts) is beneficial.⁵² Minimizing processed meats, refined carbohydrates, and sweetened beverages is also recommended.²⁰ Weight management, including losing excess weight and maintaining a healthy weight, is crucial.²⁰ Regular physical activity, aiming for at least 150 minutes per week of moderate-intensity or 75 minutes per week of vigorous-intensity activity, is advised.²⁰ Smoking cessation is a critical intervention for reducing ASCVD risk.²⁰ Alcohol consumption should be moderated, limited to no more than one drink per day for women and two for men.⁵²

Pharmacological therapy often begins with statins, which are considered the bedrock of lipid-lowering treatment for reducing ASCVD risk in both primary and secondary prevention.⁶³ High-intensity statins typically reduce LDL-C levels by at least 50%⁶¹, and the goal is to achieve the maximally tolerated dose.⁶¹ Statins are indicated for patients with severe primary hypercholesterolemia (LDL-C \geq 190 mg/dL), where high-intensity statin therapy is initiated without needing a 10-year ASCVD risk calculation.⁵⁴ For patients with clinical ASCVD, high-intensity or maximally tolerated statin therapy is recommended, aiming for an LDL-C threshold of less than 70 mg/dL.⁵⁶ In adults aged 40-75 years with diabetes mellitus and an LDL-C level of \geq 70 mg/dL, moderate-intensity statin therapy is recommended, with high-intensity statins for those at higher risk (e.g., multiple risk factors, aged 50-75 years).²⁰ For primary prevention in adults aged 40-75 years, statin therapy is considered if there is sufficient ASCVD risk after a clinician-patient discussion.²⁰ Lipid levels should be reassessed 4-12 weeks after initiating treatment, and then every 3-12 months as needed.⁵⁹ Liver transaminase levels should also be monitored.⁶² For patients experiencing statin intolerance, structured approaches like the NHS England Statin Intolerance Algorithm can guide management.⁶⁴

When statins alone are insufficient to achieve target LDL-C levels, or in cases of statin intolerance, other lipid-lowering agents are added. Ezetimibe, which reduces cholesterol absorption from the intestine, is a common add-on therapy.⁶⁴ It can reduce LDL-C by an additional 13-20% when combined with a statin⁵⁹ and is also used for patients with statin intolerance or contraindications.⁶⁴

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (e.g., alirocumab, evolocumab, inclisiran) represent a powerful class of drugs. These monoclonal antibodies prevent PCSK9 from binding to LDL receptors, thereby enhancing receptor recycling and increasing LDL-C clearance from the bloodstream.⁴⁹ PCSK9 inhibitors

can achieve significant LDL-C reductions (up to 60%) when added to statin therapy.⁴⁹ They are indicated for very high-risk patients, such as those with familial hypercholesterolemia or established ASCVD, whose LDL-C levels remain elevated despite maximally tolerated statin and ezetimibe therapy.⁴⁹ These agents may also reduce lipoprotein(a) levels.⁵⁶ Inclisiran, a small interfering RNA (siRNA) that targets PCSK9 mRNA, offers sustained LDL-C lowering with the convenience of infrequent dosing (e.g., twice-yearly injections).⁴⁹

Other lipid-lowering agents include bempedoic acid, an ATP-citrate lyase inhibitor with liver-specific action, which can reduce LDL-C by an additional 18% when added to statin therapy and is available in a fixed-dose combination with ezetimibe.⁶⁴ Fibrates and n-3 polyunsaturated fatty acids (PUFAs) are considered for the management of hypertriglyceridemia, especially in cases of very high triglyceride levels.⁵⁶

Table 4: Lipid Targets and Treatment Intensification based on ASCVD Risk (AHA/ACC vs. ESC)

Risk Category	Clinical Criteria	LDL-C Target (mg/dL)	Primary Pharmacological Strategy	Secondary Pharmacological Strategy	Tertiary Pharmacological Strategy	Guideline Reference
Very High-Risk	Established ASCVD (clinical or unequivocal on imaging); DM with target organ damage, long duration (>20 yrs), or other risk factors; eGFR <30 mL/min/1.73 m ² ; FH	<55 mg/dL (<40 mg/dL in selected recurrent ASCVD)	Maximally tolerated statin	Add Ezetimibe if target not met	Add PCSK9i if target not met	2018 AHA/ACC, 2019 ESC/EAS

	with ASCVD or another major risk factor; SCORE >10%					
High-Risk	Markedly elevated single risk factors (e.g., TC >310 mg/dL, LDL-C >190 mg/dL, BP >180/110 mmHg); FH without other risk factors; DM duration >10 yrs or with another risk factor; eGFR 30-59 mL/min/1.73 m ² ; SCORE 5%-<10%	<70 mg/dL	Maximally tolerated statin	Add Ezetimibe if target not met	Add PCSK9i if target not met	2018 AHA/ACC, 2019 ESC/EAS
Moderate-Risk	Younger DM patients (Type 1 <35 yrs; Type 2 <50 yrs) with duration	<100 mg/dL (may be considered)	Moderate-intensity statin	Consider Ezetimibe	N/A	2018 AHA/ACC, 2019 ESC/EAS

	<10 yrs, no other risk factors; SCORE 1%–<5%					
Low-Risk	SCORE <1% fatal cardiovascular disease	<116 mg/dL (may be considered)	Lifestyle modifications, consider statin based on risk discussion	N/A	N/A	2018 AHA/ACC, 2019 ESC/EAS

Complications, Prognosis, and Prevention (Atherosclerosis, ASCVD)

Uncontrolled hyperlipidemia significantly contributes to the development and progression of atherosclerosis, a condition where dangerous plaque builds up within the walls of arteries, leading to their narrowing or blockage.⁵² This atherosclerotic process is the root cause of numerous severe cardiovascular complications. These include coronary heart disease, which can manifest as chest pain (angina) or lead to a heart attack, where blood flow to a part of the heart is completely interrupted.⁴⁸ Stroke occurs when a blood clot blocks blood flow to a part of the brain.⁴⁸ Other complications include carotid artery disease, peripheral artery disease, ischemic cardiomyopathy, sudden cardiac death, erectile dysfunction, claudication, and acute limb ischemia.⁴⁸ The weakening and bulging of a blood vessel, forming an aneurysm, is also a potential consequence of high cholesterol.⁵²

The prognosis for individuals with hyperlipidemia is directly related to the duration and degree of elevated LDL cholesterol levels.⁵³ A fundamental principle in lipid management is "lower is better" for LDL-C, as evidence from randomized controlled trials consistently demonstrates that greater reductions in LDL-C lead to marked reductions in ASCVD events.⁴⁹ This principle guides the aggressive therapeutic strategies employed today.

Prevention of hyperlipidemia largely mirrors its non-pharmacological management, emphasizing the adoption and maintenance of a heart-healthy lifestyle.²⁰ This includes a balanced diet low in saturated and trans fats, regular physical activity, maintaining a healthy weight, and avoiding smoking and excessive alcohol consumption. Routine screenings are also essential for early detection and

intervention.

Recent Advancements and Emerging Therapies

The field of hyperlipidemia treatment continues to advance, driven by the persistent challenge of patients who do not achieve target lipid levels or cannot tolerate traditional therapies like statins.⁴⁹ This unmet need has spurred the development of several novel therapeutic approaches.

A significant recent development is the emergence of **oral PCSK9 inhibitors**. For instance, AZD0780, an investigational once-daily oral PCSK9 inhibitor, demonstrated a statistically significant 50.7% reduction in LDL-C at 12 weeks when added to standard-of-care statin therapy in the Phase IIb PURSUIT trial.⁶⁷ This oral formulation offers the potential for a convenient daily option to help patients reach their guideline-recommended LDL-C targets (<70 mg/dL), addressing a major barrier to adherence associated with injectable therapies.⁶⁷

Combination therapies are also showing enhanced efficacy. A Phase 3 clinical trial demonstrated that the combination of obicetrapib with ezetimibe reduced LDL-C levels by 48.6% after approximately three months in high-risk patients who were not at their target despite maximal lipid-lowering therapy. This combination proved more effective than either drug administered alone.⁶⁸ Research is also ongoing to determine if combining bempedoic acid with ezetimibe or a PCSK9 inhibitor can achieve lower LDL-C levels more rapidly and with an improved safety profile than monotherapy.⁴⁹

Beyond existing drug classes, **gene editing and RNA interference (RNAi)** technologies hold immense promise for revolutionizing dyslipidemia treatment. Gene editing involves making precise alterations to an organism's DNA to modify gene expression, offering a potential long-term solution for genetic lipid disorders.⁶⁵ RNAi therapies, such as inclisiran (which targets PCSK9 mRNA), work by turning off or decreasing the activity of specific genes. Inclisiran, an siRNA drug, has shown sustained LDL-C lowering with the convenience of twice-yearly injections, significantly reducing treatment burden and improving compliance.⁴⁹ These advanced therapies are currently in various stages of clinical trials, with inclisiran being in advanced stages.⁴⁹ Furthermore, research continues to explore other novel targets beyond PCSK9 for lipid management, indicating a future of increasingly personalized and effective interventions.⁶⁵

The consistent emphasis on the "lower is better" paradigm for LDL-C, supported by robust evidence from randomized controlled trials showing marked reductions in ASCVD events with aggressive LDL-C lowering, has profound implications for clinical

practice.⁴⁹ This principle dictates an aggressive, multi-modal approach to lipid management, justifying the sequential addition of therapies (statins, ezetimibe, PCSK9 inhibitors) to achieve increasingly lower LDL-C targets, especially in high-risk individuals. For clinicians, this means that achieving "normal" LDL-C levels may not be sufficient if a patient presents with significant ASCVD risk. It necessitates a willingness to escalate therapy beyond statins, even considering the higher costs associated with newer agents, to proactively prevent cardiovascular events. This represents a shift towards a more intensive and proactive management strategy aimed at maximizing patient benefit.

The recognition that a significant proportion of patients either fail to achieve target lipid levels or cannot tolerate conventional statin therapy underscores a critical unmet need in hyperlipidemia management. The development of novel therapies, including oral PCSK9 inhibitors, bempedoic acid, and various combination regimens, directly addresses this challenge.⁴⁹ This expansion of the therapeutic arsenal provides clinicians with viable alternatives for patients who experience statin-related side effects or whose LDL-C remains elevated despite maximal statin therapy. The emergence of oral PCSK9 inhibitors and infrequent dosing siRNA therapies also holds significant promise for improving patient adherence and convenience, factors that are crucial for the long-term success of chronic disease management. This evolution in treatment options suggests a future where lipid management is more tailored and accessible to a broader range of patients, ultimately leading to improved overall cardiovascular outcomes.

5. Asthma

Etiology, Pathophysiology, and Global Epidemiology

Asthma is a chronic inflammatory condition of the airways characterized by variable expiratory airflow limitation, heightened airway hyperresponsiveness, and persistent inflammation.⁶⁹ During an asthma flare-up, the airways narrow, swell, and may produce excessive mucus, significantly impeding the movement of air in and out of the lungs and leading to characteristic symptoms.⁶⁹

The global prevalence of asthma is substantial, affecting over 300 million individuals worldwide according to Global Initiative for Asthma (GINA) guidelines.⁷³ In 2021, an estimated 260 million people globally were living with asthma.⁷³ The prevalence in the adult population ranges from 1% to 21%, and up to 20% in children.⁷⁵

The development and exacerbation of asthma are influenced by a complex interplay of genetic and environmental factors. Genetic predisposition plays a significant role,

with a family history of allergies or asthma increasing an individual's susceptibility.⁶⁹ Asthma onset before the age of 12 years is more likely to be influenced by genetic factors.⁷⁶ Environmental factors and allergens are major triggers. These include air pollution (e.g., traffic pollution, high ozone levels), occupational asthmagens (e.g., ammonia, latex, pesticides, metal or wood dusts, formaldehyde, isocyanate paint), exposure to indoor volatile organic compounds (e.g., phthalates), gas stoves, and both active and secondhand tobacco smoke exposure (including during pregnancy).⁶⁹ Common indoor allergens such as dust mites, cockroaches, animal dander, and mold also contribute to symptoms.⁷⁶ Certain viral respiratory infections, notably respiratory syncytial virus (RSV) and rhinovirus, acquired in early childhood, may increase the risk of developing asthma.⁷⁶ Other contributing factors include being overweight or obese, strong emotional states and stress, sulfites and preservatives found in some foods, gastroesophageal reflux disease (GERD), and certain medications like beta-blockers, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs).⁶⁹ Maternal psychological stress during pregnancy has also been identified as a risk factor for the child developing asthma.⁷⁶ The "hygiene hypothesis" suggests that reduced exposure to non-pathogenic bacteria and viruses in early childhood, due to increased cleanliness, may contribute to the rising rates of asthma.⁷⁶

At a pathophysiological level, the airways in individuals with asthma are characterized by chronic inflammation, which intensifies during flare-ups, leading to increased swelling.⁶⁹ This inflammation reduces the radius of the airway lumen and increases the work of breathing.⁷⁰ Airway hyperresponsiveness causes the airways to constrict excessively in response to various triggers.⁷² An asthma exacerbation typically involves two phases:

- **Early Phase:** Triggered by IgE antibodies, which are sensitized to specific environmental allergens and bind to high-affinity mast cells and basophils. Upon exposure to the allergen, mast cells rapidly de-granulate, releasing inflammatory mediators such as histamine, prostaglandins, leukotrienes, and cytokines.⁷⁰
- **Late Phase:** Occurs several hours later, characterized by the recruitment and localization of eosinophils, basophils, neutrophils, and helper and memory T-cells to the lungs, leading to further bronchoconstriction and sustained inflammation.⁷⁰

Chronic inflammation can also lead to irreversible structural changes in the airways, a process known as airway remodeling. This includes fibrosis, excessive mucus secretion, epithelial cell injury, hypertrophy of airway smooth muscle, increased thickening of the basement membrane, and angiogenesis.⁷⁰ Airway remodeling can result in permanent airflow obstruction, making breathing persistently difficult.⁶⁹

Clinical Presentation, Diagnostic Criteria, and Severity Classification

Asthma symptoms exhibit considerable variability among individuals, both in frequency and intensity.⁶⁹ The most common symptoms include wheezing, often described as a scratchy or whistling sound, particularly during exhalation, which is a hallmark sign in children.⁶⁹ Other prevalent symptoms are coughing (which can be chronic and often worsens with respiratory viral infections), shortness of breath, a sensation of chest tightness or pain, and disrupted sleep due to these respiratory symptoms.⁶⁹ Symptoms may occur infrequently, only during specific activities such as exercise (exercise-induced bronchoconstriction or asthma, EIB/EIA), or they may be persistent.⁶⁹ Indicators that asthma is worsening include an increase in the frequency and bothersomeness of symptoms, escalating difficulty breathing (quantified by a peak flow meter), and a more frequent need for quick-relief inhalers.⁶⁹

The diagnosis of asthma is based on a comprehensive assessment involving a history of characteristic symptom patterns and objective evidence of variable expiratory airflow limitation.⁷² The diagnostic process typically includes:

- **Medical History and Physical Examination:** Clinicians inquire about recurrent episodes of cough, wheezing, difficulty breathing, and chest tightness, as well as triggers that worsen symptoms (e.g., night, exercise, allergens, irritants, weather changes, stress) and a family history of allergies or asthma.⁷¹ Auscultation of the chest may reveal wheezing, particularly on expiration.⁷⁹
- **Spirometry:** This is the primary diagnostic test for individuals aged 5 years and older.⁷⁹ Spirometry measures the volume of air inhaled and exhaled and the rate of airflow.⁷⁹ A key finding is that airway obstruction should be at least partially reversible with an inhaled bronchodilator.⁷⁹ If spirometry results are normal but asthma is strongly suspected, bronchial hyperresponsiveness testing, such as a methacholine challenge test, may be used to provoke symptoms and confirm hyperreactivity.⁷⁹
- **Peak Expiratory Flow (PEF) Monitoring:** Serial measurements of PEF can be valuable for evaluating work-related asthma or monitoring disease control over time.⁷²
- **Fractional Exhaled Nitric Oxide (FeNO):** This test measures nitric oxide gas in the breath, which is a marker of allergic airway inflammation. Elevated FeNO levels support a diagnosis of allergic asthma, although they do not differentiate between work-related and non-work-related asthma. A normal FeNO level does not rule out asthma.⁷²
- **Allergy Testing:** Skin prick tests or blood tests can help identify specific allergic triggers that may be contributing to or worsening asthma symptoms.⁷⁹

- **Differential Diagnosis:** In adults, the differential diagnosis for asthma symptoms includes, but is not limited to, chronic obstructive pulmonary disease (COPD), non-asthmatic eosinophilic bronchitis, hypersensitivity pneumonitis, vocal cord dysfunction, and obliterative bronchiolitis.⁸¹

Asthma severity is classified to guide initial treatment and ongoing management. The GINA guidelines assess asthma control across two domains: symptom control (frequency of symptoms, night awakenings, activity limitation, and short-acting beta-agonist (SABA) use) and the risk of adverse outcomes (particularly exacerbations, persistent airflow limitation, and medication side effects).⁷² The National Asthma Education and Prevention Program (NAEPP) classifies severity initially based on clinical signs, symptoms, and peak flow or spirometry, and then, once the condition is stable, by the level of medication required to maintain treatment goals.⁸² Severity is typically categorized as intermittent, mild persistent, moderate persistent, or severe persistent.⁸⁰

Management Strategies

The primary goals of asthma management are to achieve and sustain asthma control, minimize exacerbations, reduce hospitalizations and fatalities, and ultimately enhance the patient's quality of life.⁷⁶

Non-pharmacological interventions, particularly the identification and avoidance of asthma triggers, are considered the most effective treatment strategy.⁷⁶ Patients should be educated to identify and minimize exposure to common allergens (e.g., pet dander, dust mites, pollen, mold) and irritants (e.g., tobacco smoke, air pollution, cold air, chemical fumes).⁶⁹

Pharmacological therapy for asthma has seen significant updates, notably in the GINA 2024 guidelines. A critical change is the recommendation that all adults and adolescents with asthma should receive inhaled corticosteroid (ICS)-containing medication and should **not** be treated with short-acting beta agonist (SABA) alone.⁸³ This is based on evidence that regular SABA use, even for short durations, can lead to detrimental effects such as beta-receptor downregulation, diminished broncho-protection, and rebound hyper-responsiveness. Increased SABA usage correlates with a heightened risk of exacerbations and mortality.⁸⁴

The GINA 2024 strategy divides treatment into two "Tracks":

- **Track 1 (Preferred):** The reliever medication is an as-needed combination of low-dose ICS-formoterol (e.g., budesonide-formoterol).⁸³ This approach has been

shown to reduce the occurrence of serious exacerbations, fatalities, and hospitalizations.⁸⁴

- **Track 2:** Utilizes SABA as the reliever along with a separate ICS inhaler.⁸³

A stepwise approach is generally employed to achieve and maintain asthma control, gradually increasing medication dosage or type as needed.⁸⁴ Initial treatment for mild intermittent asthma, according to older NAEPP guidelines, involved no daily medicine with SABA as needed.⁸² However, GINA 2024 now advises an ICS-containing reliever for all patients.⁸³ For mild persistent asthma, low-dose inhaled steroids are preferred, with alternatives including leukotriene modifiers, cromolyn, nedocromil, or sustained-release theophylline.⁸² Moderate persistent asthma typically requires a low-to-medium dose of ICS combined with a long-acting beta2-agonist (LABA).⁸² Severe persistent asthma often necessitates high-dose ICS plus LABA, with the potential addition of oral corticosteroids if needed.⁸² If symptoms persist despite these measures, additional long-acting muscarinic antagonists (LAMA) and biologic agents may be introduced.⁸⁴

Oral corticosteroids are added for moderate to severe exacerbations.⁸² However, long-term systemic steroid use carries significant side effects, including an increased risk of diabetes, osteoporosis, and adrenal insufficiency.⁷⁸

Biologic therapies represent a significant advancement for severe asthma, offering targeted treatment for specific inflammatory phenotypes. These include omalizumab (anti-IgE), mepolizumab and reslizumab (anti-IL-5), benralizumab (anti-IL-5 receptor), dupilumab (anti-IL-4/IL-13), and tezepelumab (anti-TSLP).⁸⁷ Biologics can reduce the need for oral steroids and significantly improve quality of life.⁷⁸ Omalizumab is indicated for uncontrolled allergic asthma with elevated IgE, while mepolizumab is used for severe eosinophilic asthma.⁸⁸ Home self-administration of biologics has enhanced accessibility, but requires proper patient training and ongoing clinical monitoring.⁸⁷ Tiotropium, a long-acting anti-muscarinic agent, has also shown efficacy in reducing exacerbations in patients with poorly controlled asthma despite ICS/LABA therapy.⁸⁸

A crucial component of effective asthma management is a personalized **Asthma Action Plan**. This written guide provides patients with clear instructions on medication schedules, helps them recognize worsening asthma control, and directs treatment modifications based on changes in symptoms and home peak expiratory flow measurements.⁸³ Additionally, regular vaccinations against influenza and pneumonia are important preventive measures to avoid triggering asthma flare-ups.⁶⁹

Table 5: Asthma Severity Classification and Corresponding Initial Treatment Steps (GINA/NAEPP)

Asthma Classification	Symptom Frequency (Typical)	Lung Function Criteria (Typical)	Initial Treatment Recommendation (GINA 2024)	Quick-Relief Medication (GINA 2024)	Key Considerations
Intermittent	Daytime symptoms <2x/week; Nighttime awakenings <2x/month; SABA use <2x/week	FEV1 >80% predicted; FEV1/FVC normal	Low-dose ICS-formoterol as needed (Track 1 preferred) OR Low-dose ICS daily + SABA as needed (Track 2)	Low-dose ICS-formoterol as needed (Track 1) OR SABA as needed (Track 2)	Avoid SABA monotherapy; risk of exacerbations even in mild asthma.
Mild Persistent	Daytime symptoms ≥2x/week but not daily; Nighttime awakenings ≥2x/month; SABA use ≥2x/week but not daily	FEV1 >80% predicted; FEV1/FVC normal	Low-dose ICS-formoterol as needed (Track 1 preferred) OR Low-dose ICS daily + SABA as needed (Track 2)	Low-dose ICS-formoterol as needed (Track 1) OR SABA as needed (Track 2)	Daily ICS is cornerstone; consider leukotriene modifiers as alternative.
Moderate Persistent	Daily daytime symptoms; Nighttime awakenings >1x/week; SABA use daily	FEV1 60-80% predicted; FEV1/FVC reduced by 5%	Low-dose ICS-formoterol daily + as needed (Track 1 preferred) OR Medium-dose ICS daily + LABA +	Low-dose ICS-formoterol as needed (Track 1) OR SABA as needed (Track 2)	Combination ICS/LABA is preferred; consider step-up to medium-dose ICS.

			SABA as needed (Track 2)		
Severe Persistent	Symptoms throughout the day; Nighttime awakenings frequent; SABA use multiple times daily	FEV1 <60% predicted; FEV1/FVC reduced by >5%	High-dose ICS-formoterol daily + as needed (Track 1 preferred) OR High-dose ICS daily + LABA + SABA as needed (Track 2)	Low-dose ICS-formoterol as needed (Track 1) OR SABA as needed (Track 2)	Consider LAMA, oral corticosteroids, or biologic agents; refer to specialist.

Complications, Prognosis, and Prevention

Uncontrolled asthma can lead to a range of significant long-term complications, severely impacting a patient's health and quality of life. Chronic inflammation in the airways, if left unmanaged, can result in irreversible structural changes known as airway remodeling. This process involves scarring, thickening, narrowing, and fibrosis of the airways, leading to permanent impairment of breathing function.⁶⁹ Long-term severe asthma can also contribute to the development of chronic obstructive pulmonary disease (COPD) or asthma-COPD overlap syndrome (ACO).⁷⁸

Frequent and severe asthma exacerbations are a direct consequence of uncontrolled disease, often necessitating oral corticosteroids, emergency room visits, or hospitalization.⁷⁷ Individuals with uncontrolled asthma may also face an increased risk of developing pneumonia due to existing lung damage or weakened lung tissue.⁷⁷ Disrupted sleep is a common issue, as airway restriction, coughing, and wheezing can significantly interfere with a patient's ability to achieve restful sleep.⁶⁹ There is also a bidirectional relationship with gastroesophageal reflux disease (GERD); asthma increases the risk of GERD, and GERD, in turn, can worsen asthma symptoms by irritating the lungs and airways.⁶⁹ For pregnant women, severe, uncontrolled asthma can lead to serious complications for both mother and child, including high blood pressure, preeclampsia, premature delivery, and decreased fetal oxygen levels.⁷⁷ The physical limitations imposed by uncontrolled asthma symptoms, such as shortness of breath and wheezing, can make exercise and weight loss efforts challenging, thereby

contributing to obesity.⁷⁷ Furthermore, individuals with asthma exhibit higher rates of anxiety, psychological stress, and depression, which can paradoxically lead to poorer asthma control, creating a vicious cycle.⁷⁶

While there is currently no known cure for asthma, its symptoms can typically be well-controlled with appropriate management.⁷⁶ However, suboptimal control remains common globally.⁷⁶ Prevention strategies primarily involve identifying and avoiding triggers, diligently adhering to a personalized asthma action plan, ensuring up-to-date vaccinations, and effectively managing any co-existing medical conditions.⁶⁹

Recent Advancements and Emerging Therapies

Recent advancements in asthma treatment, particularly for severe forms, offer new hope for improved control and quality of life. **Biologic therapies** have emerged as a significant breakthrough, providing targeted treatment for specific inflammatory phenotypes of severe asthma.⁸⁷ These agents, including omalizumab (anti-IgE), mepolizumab and reslizumab (anti-IL-5), benralizumab (anti-IL-5 receptor), dupilumab (anti-IL-4/IL-13), and tezepelumab (anti-TSLP), can reduce the need for systemic steroids and significantly enhance patient quality of life.⁷⁸ Omalizumab, for instance, is used for uncontrolled allergic asthma with elevated IgE levels, while mepolizumab targets severe eosinophilic asthma.⁸⁸ The ability for patients to self-administer some biologics at home has greatly improved accessibility, though proper training and ongoing clinical monitoring remain crucial.⁸⁷

Bronchial thermoplasty (BT) is a non-pharmacological treatment option for severe asthma. This procedure aims to reduce airway smooth muscle mass.⁸⁸ While it has shown modest benefits in improving quality of life and reducing exacerbations, patients may experience increased morbidity during and shortly after the treatment.⁸⁹ Its precise role in the management algorithm is still being defined, sometimes considered for patients with non-Type 2 inflammation or those who do not respond favorably to biologic therapies.⁸⁹

Novel oral therapies are also under investigation. **Rilzabrutinib**, an investigational oral Bruton's tyrosine kinase (BTK) inhibitor, has shown promising results in a Phase 2 study for adult patients with uncontrolled moderate-to-severe asthma.⁹⁰ BTK plays a critical role in B cells and mast cells, key players in immune-mediated processes.⁹⁰ The study demonstrated a numerical reduction in loss of asthma control events and improvements in symptoms, with a good tolerability profile and no new safety signals. These encouraging results support the advancement of rilzabrutinib into a Phase 3

clinical development program.⁹⁰

The definitive statement in the GINA 2024 guidelines, advising that all adults and adolescents with asthma should receive inhaled corticosteroid (ICS)-containing medication and **should not be treated with short-acting beta agonist (SABA) alone**, marks a pivotal shift in asthma management.⁸³ This directive is predicated on robust evidence demonstrating that increased SABA usage correlates directly with adverse clinical outcomes, including a heightened risk of exacerbations and mortality, due to mechanisms such as beta-receptor downregulation and rebound hyper-responsiveness.⁸⁴ This change necessitates a fundamental re-education of patients who may have historically relied solely on SABAs for symptom relief. Clinicians must now emphasize the indispensable role of ICS in addressing the underlying airway inflammation, even in seemingly mild asthma, by promoting ICS-containing regimens (e.g., as-needed ICS-formoterol or separate daily ICS with SABA for rescue). This strategic adjustment is poised to significantly reduce the burden of asthma exacerbations, leading to fewer hospitalizations and fatalities, and ultimately improving long-term disease control and patient outcomes.

The strong bidirectional relationship between asthma and various comorbidities, such as gastroesophageal reflux disease (GERD), obesity, anxiety, depression, and chronic obstructive pulmonary disease (COPD), underscores the necessity of a holistic and integrated approach to asthma care.⁶⁹ For example, anxiety can exacerbate asthma symptoms, and conversely, uncontrolled asthma can heighten anxiety levels.⁹¹ Similarly, the long-term use of systemic corticosteroids, often necessary for severe asthma, can predispose patients to conditions like diabetes and osteoporosis.⁷⁸ This interconnectedness implies that effective asthma management extends beyond pulmonary interventions alone. Clinicians are encouraged to actively screen for and manage these co-existing conditions, as their presence can significantly impact asthma control and the overall patient prognosis. Addressing these comorbidities can lead to improved asthma outcomes and a reduction in the overall burden of disease, often requiring multidisciplinary collaboration to optimize patient care.

6. Depression and Anxiety Disorders

Etiology, Pathophysiology, and Global Epidemiology

Depression, particularly Major Depressive Disorder (MDD), is a mood disorder characterized by persistent feelings of sadness, emptiness, or hopelessness, coupled with a profound loss of interest or pleasure in activities previously enjoyed.⁹² It significantly affects an individual's thoughts, feelings, and behaviors, and is distinct from transient sadness or the natural grieving process.⁹² Anxiety disorders, such as

Generalized Anxiety Disorder (GAD), involve more than occasional worry or fear. The anxiety is persistent, often unsubstantiated, experienced across multiple situations, and can worsen over time, significantly disrupting daily life.⁹⁷

The global prevalence of these mental health conditions is substantial. A 2023 national survey indicated that nearly 3 in 10 US adults have been diagnosed with depression at some point, with approximately 18% currently experiencing it.⁹² Globally, in 2019, an estimated 280 million people suffered from depression, making it the second-leading cause of disability worldwide.⁹⁹ Anxiety disorders affected approximately 301 million people globally in 2019, ranking as the eighth-leading cause of disability.⁹⁹ The lifetime risk of experiencing at least one episode of depression or anxiety is estimated at 15-18%.⁹⁹ Demographic data reveal that women are more likely than men, and younger adults are more likely than older adults, to experience both depression and anxiety, with susceptibility often beginning before age 15.⁹² The COVID-19 pandemic has also led to a noticeable and disproportionate increase in the global burden of depressive and anxiety disorders.¹⁰⁰

The etiology of depression and anxiety disorders is complex, involving a multifaceted interplay of biological, genetic, environmental, and psychological factors. Biologically, imbalances in brain chemicals, particularly neurotransmitters like serotonin, dopamine, and norepinephrine, are thought to play a crucial role in mood regulation.⁹² Physical changes in brain structure and chemistry, as well as disruptions in neurocircuits, have been observed in individuals with depression.⁹³ Hormonal fluctuations associated with pregnancy, postpartum periods, menopause, and thyroid disorders can also contribute to or trigger depressive episodes.⁹³ Genetic predisposition is evident, as these conditions often run in families; for instance, if one identical twin has depression, the other has a 70% chance of developing it.⁹²

Environmental and social factors significantly influence risk. Continuous exposure to adverse conditions such as violence, neglect, abuse, or poverty can increase vulnerability.⁹² Stressful and traumatic life events, including bereavement, work-related difficulties, relationship changes, financial problems, and significant medical concerns, are common triggers.⁹⁴ A lack of adequate social support and experiences of discrimination also contribute to risk.⁹³ Psychologically, negative thought patterns and maladaptive coping behaviors, such as avoidance and substance use, can heighten vulnerability to depression.⁹³

Furthermore, various comorbid medical conditions can increase the risk or worsen the course of depression and anxiety. These include chronic physical illnesses like diabetes, heart disease, chronic pain, and chronic obstructive pulmonary disease

(COPD).⁹¹ Other mental health conditions, such as bipolar disorder and personality disorders, frequently co-occur.⁹⁷ Certain medications, including corticosteroids, beta-blockers, statins, hormonal birth control, opioids, and some decongestants, can induce depressive symptoms.⁹⁴ Illicit drug and alcohol use, head injuries, and neurodegenerative diseases like Alzheimer's and Parkinson's also contribute to risk.⁹⁴

Clinical Presentation, Diagnostic Criteria (DSM-5), and Differential Diagnosis

The clinical presentation of Major Depressive Disorder (MDD) is defined by specific diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). For a diagnosis of MDD, an individual must experience five or more characteristic symptoms during the same two-week period, representing a significant change from previous functioning. Crucially, either a depressed mood or a loss of interest/pleasure (anhedonia) must be among these symptoms.⁹²

Core symptoms of MDD include:

- **Depressed mood:** Feeling sad, empty, or hopeless for most of the day, nearly every day. In children and adolescents, this may manifest as irritable mood.⁹²
- **Loss of interest/pleasure:** A markedly diminished interest or pleasure in all, or almost all, activities for most of the day, nearly every day.⁹²
- **Significant weight change:** Unintentional weight loss or gain of more than 5% of body weight in a month, or a noticeable decrease or increase in appetite nearly every day.⁹²
- **Sleep disturbances:** Insomnia (difficulty falling or staying asleep) or hypersomnia (sleeping excessively) nearly every day.⁹²
- **Psychomotor agitation or retardation:** Observable restlessness or slowed movements and speech, not merely subjective feelings.⁹²
- **Fatigue or loss of energy:** Feeling tired or lacking energy nearly every day.⁹²
- **Feelings of worthlessness or excessive/inappropriate guilt:** These feelings are present nearly every day and are not merely self-reproach or guilt about being ill.⁹²
- **Decreased concentration:** Difficulty thinking, concentrating, or making decisions nearly every day.⁹²
- **Thoughts of death/suicide:** Recurrent thoughts of death (beyond fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for suicide.⁹²

The symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.¹⁰³ Furthermore, the episode must not be attributable to the physiological effects of a substance or another

medical condition, nor be better explained by other psychotic disorders. There should also be no history of manic or hypomanic episodes, unless they were substance-induced or attributable to a medical condition.¹⁰³

Generalized Anxiety Disorder (GAD) is characterized by excessive anxiety and worry, occurring more days than not for at least 6 months, about a variety of things or situations, associated with three or more of the following six symptoms (only one symptom is required in children)⁹⁷:

- Restlessness or feeling keyed up or on edge.⁹⁷
- Being easily fatigued.⁹⁷
- Difficulty concentrating or the mind going blank.⁹⁷
- Irritability.⁹⁷
- Muscle tension.⁹⁷
- Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).⁹⁷

Similar to MDD, the symptoms of GAD must cause clinically significant distress or impairment in important areas of functioning and not be attributable to the physiological effects of a substance or another medical condition, nor be better explained by another mental disorder.⁹⁷

The diagnostic process for mental health conditions begins with a thorough clinical interview, including questions about symptoms, medical history, and a physical examination.¹⁰⁵ A crucial step is developing a **differential diagnosis**, which is a list of possible conditions that share similar symptoms.¹⁰² For depression, this differential may include anxiety disorders, bipolar disorder, dementia, and hypothyroidism.¹⁰⁵ For anxiety, it can include other anxiety disorders, depression, and substance abuse problems.⁹⁷ It is essential to rule out malingering, factitious disorder, and drug-related causes (both prescription and illicit drugs) that can mimic depressive or anxious symptoms.¹⁰² Laboratory tests (blood or urine) and imaging studies may be ordered to exclude underlying medical conditions or substance use.¹⁰² A definitive diagnosis typically requires symptoms to be present for most of the day, nearly every day, for more than two weeks.⁹²

Management Strategies

The management of depression and anxiety disorders is tailored to the individual, often involving a combination of approaches and prioritizing shared decision-making, where patients are actively involved in discussions and informed choices about their care.¹⁰⁶

Psychotherapy, or "talk therapy," is frequently a first-line treatment or used in conjunction with medication.⁹⁵

- **Cognitive Behavioral Therapy (CBT)** has a strong evidence base for treating symptoms of depression and anxiety. It teaches individuals to identify and change unhelpful thought patterns and behaviors to improve their emotional state. CBT is often time-limited and structured.⁹⁵
- **Interpersonal Therapy (IPT)** focuses on improving problems in personal relationships and addressing life changes that may contribute to mood disturbances. IPT is also typically time-limited.⁹⁵ Other forms of psychotherapy, such as psychodynamic therapy, may also be beneficial for some individuals.⁹⁵

Pharmacological therapy often involves antidepressants, which are the most common medications prescribed for depression.¹⁰⁷ Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, sertraline, paroxetine, and citalopram, are frequently used.¹⁰⁷ It is important to note that antidepressants typically take 2-4 weeks to begin having an effect and up to 12 weeks to reach their full therapeutic potential.¹⁰⁷ In some cases, mood stabilizers or antipsychotic medications may be used.¹⁰⁷ NICE guidelines advocate for a stepped-care approach, initiating with less intensive interventions for mild depression.¹⁰⁶ When discontinuing antidepressant medication, patients should be monitored for mild withdrawal symptoms, which are common and usually time-limited, and advised to contact their prescriber if symptoms persist or worsen.¹⁰⁶

Brain stimulation therapies are considered for treatment-resistant depression, where other interventions have not been effective.¹⁰⁷

- **Electroconvulsive Therapy (ECT)** involves transmitting short electrical impulses into the brain and can cause side effects, including memory loss.¹⁰⁷
- **Repetitive Transcranial Magnetic Stimulation (rTMS)** is a non-invasive technique that uses a magnet to activate specific brain regions. Newer accelerated protocols, such as SAINT-iTBS, have significantly shortened treatment courses to as little as 5 days, demonstrating high response and remission rates.¹⁰⁸ Side effects are generally mild, including headaches and dizziness, with seizures being extremely rare.¹⁰⁸

Lifestyle modifications play a supportive role in managing depression and anxiety. Regular physical activity, even 30 minutes of daily walking, can improve mood.⁹⁵ Maintaining a regular bedtime and wake-up time, consuming healthy meals, connecting with trusted individuals, managing stress, and avoiding alcohol, nicotine, and illicit drugs are all beneficial strategies.⁹⁵ **Psychoeducation and support groups**

are also valuable, providing patients and their families with information about the illness, coping strategies, and a platform for sharing experiences.¹⁰⁷

Complications, Prognosis, and Prevention

Untreated depression and anxiety disorders can lead to a cascade of significant complications, impacting various aspects of an individual's life. A primary consequence is functional impairment, interfering with daily activities, work or school performance, and personal relationships.⁹² These conditions frequently co-occur with other mental disorders, including major depression, anxiety disorders, substance misuse, bipolar disorder, and personality disorders, complicating diagnosis and treatment.⁹⁵

Beyond mental health, untreated depression and anxiety can profoundly affect physical health. They can worsen existing chronic illnesses such as diabetes, cancer, heart disease, and chronic pain.⁹⁵ Chronic anxiety, specifically, is linked to digestive disorders like irritable bowel syndrome (IBS) and functional dyspepsia, heart disease (increasing the risk of cardiovascular events and stroke), and can exacerbate asthma and other breathing problems, creating a cyclical worsening of symptoms.⁹¹

A critical and severe complication is the increased risk of suicidal thoughts and behaviors.⁹² Suicide is a leading cause of death, particularly among adolescents.¹⁰⁰ Long-term effects of untreated conditions include the chronicity of symptoms; for instance, persistent depressive disorder can last for years with fluctuating symptoms that rarely disappear for extended periods, and untreated GAD often becomes chronic.⁹⁷

Despite these potential complications, depression is a very treatable condition.⁹² For individuals with recurrent episodes or a strong family history, longer-term maintenance treatment may be recommended to reduce the risk of future relapses.⁹² Prevention efforts focus on promoting mental health awareness, early recognition of symptoms, and ensuring timely access to appropriate care.⁹⁶ Adopting healthy behaviors, including regular exercise, maintaining a consistent sleep schedule, consuming a nutritious diet, and fostering social connections, also plays a vital role in prevention and overall well-being.⁹⁵

Recent Advancements and Emerging Therapies

The landscape of treatment for depression and anxiety disorders is undergoing rapid evolution, with significant advancements in novel therapies, particularly for treatment-resistant cases.

Ketamine therapy has emerged as a rapid-acting antidepressant, demonstrating efficacy within hours for severe and treatment-resistant depression (TRD) and for alleviating suicidal thoughts.¹⁰⁸ Its hypothesized mechanism involves blocking glutamate from binding to NMDA receptors, thereby regulating communication between nerve cells, and stimulating the production of brain-derived neurotrophic factor (BDNF), which promotes neuroplasticity and helps change negative thought patterns.¹⁰⁸ Ketamine is typically administered intravenously or intranasally (esketamine) and should be combined with other treatments, such as antidepressants and psychotherapy, for sustained results.¹⁰⁸ Newer protocols, including at-home ketamine administration under remote supervision, are increasing accessibility.¹¹² Research is also exploring ketamine metabolites, such as RR-HNK, which have shown antidepressant effects in preclinical studies without the sedative or dissociative side effects of ketamine, demonstrating a promising safety profile in early human trials.¹¹¹

Psychedelic-assisted therapies are gaining traction, with the FDA having approved MDMA-assisted therapy and psilocybin for severe depression when used in controlled therapeutic settings.¹¹⁰ These substances, when integrated with traditional psychotherapy methods, have shown remarkable results, enhancing the effectiveness of both approaches. For example, a study found that psilocybin-assisted therapy combined with cognitive behavioral therapy led to a 40% higher improvement rate compared to CBT alone.¹¹² Therapists are receiving specialized training to guide patients through these experiences and help integrate insights into daily life, aiming for sustained recovery by addressing underlying psychological issues.¹¹²

Precision psychiatry is revolutionizing depression treatment by moving away from a one-size-fits-all approach. This involves using genetic testing to enhance medication selection and employing AI algorithms to improve treatment recommendations, leading to significant improvements in treatment success rates, especially for TRD.¹¹²

Transcranial Magnetic Stimulation (TMS) continues to evolve as a non-invasive treatment modality. Latest TMS devices offer more precise targeting and shorter treatment sessions. Accelerated TMS protocols, such as SAINT-iTBS, have significantly condensed treatment duration to just one week, with reported response rates of approximately 85% and remission rates of around 78% within five days of treatment.¹⁰⁸ TMS is generally safe and well-tolerated, with mild side effects like headaches and dizziness, and a very low risk of seizures.¹⁰⁸

Other emerging areas include the use of **Virtual Reality (VR) therapy** interventions, which have shown positive effects in improving anxiety states.¹¹² Research is also exploring novel compounds like Tianeptine, an atypical antidepressant used clinically

in Europe, Asia, and South America, which has a different mechanism of action than currently approved antidepressants in the US and is being investigated for its efficacy in patients who have failed previous treatments.¹¹⁰

The rapid advancements in depression and anxiety treatment, particularly the emergence of fast-acting and novel mechanism-based therapies like ketamine and psychedelic-assisted therapies, highlight a critical shift in the management paradigm for severe and treatment-resistant conditions. Traditional antidepressants often take weeks to months to show effect, leaving patients with severe, life-threatening symptoms in prolonged distress.¹¹¹ The availability of therapies that can induce significant symptom reduction within hours or days represents a profound improvement in acute care and crisis intervention. This evolution necessitates that clinicians stay abreast of these developments, understanding their mechanisms, appropriate patient selection, and the need for integration with traditional psychotherapy for sustained benefits. It also underscores the importance of a multidisciplinary approach, potentially involving specialized clinics for these advanced treatments, to provide rapid and effective relief for individuals who have historically had limited options.

The strong interconnectedness between mental health conditions and physical health, where depression and anxiety can worsen chronic illnesses like diabetes, heart disease, and asthma, while chronic physical conditions can also precipitate or exacerbate mental health disorders, emphasizes the need for truly integrated care.⁹¹ This bidirectional relationship means that treating one condition in isolation may lead to suboptimal outcomes for both. For clinicians, this implies the necessity of routine mental health screening in patients with chronic physical illnesses, and conversely, screening for physical comorbidities in patients presenting with mental health concerns. A holistic approach that addresses both physical and mental well-being simultaneously can lead to improved overall patient outcomes, reduced disease burden, and enhanced quality of life, underscoring the importance of collaborative care models between primary care physicians and mental health specialists.

Conclusions

The comprehensive review of common chronic illnesses in primary care—Hypertension, Type 2 Diabetes Mellitus, Hyperlipidemia, and Depression/Anxiety Disorders—underscores their pervasive impact on global health and the critical role of primary care providers in their management. These conditions, often asymptomatic in early stages, necessitate proactive screening and a nuanced understanding of their

complex etiologies, pathophysiologies, and diverse clinical presentations.

A significant observation across these conditions is the evolving nature of diagnostic and treatment guidelines. The redefinition of hypertension thresholds by AHA/ACC, for instance, has broadened the scope of diagnosis, highlighting the increased risk associated with previously considered "elevated" blood pressure. Similarly, the shift in diabetes management towards agents offering cardiorenal protection beyond glycemic control, and the GINA 2024 guidelines' strong recommendation against SABA monotherapy for asthma, reflect a growing emphasis on holistic, complication-preventing strategies. These changes necessitate continuous clinical education and adaptation to ensure optimal patient care.

The pervasive influence of lifestyle factors—diet, physical activity, weight management, and smoking cessation—is a consistent theme across all reviewed conditions. These non-pharmacological interventions form the foundational bedrock of both prevention and management, often preceding or complementing pharmacological approaches. The interconnectedness of these chronic diseases is also evident; conditions like obesity, chronic stress, and inflammation emerge as common risk factors, and comorbidities frequently exacerbate each other, underscoring the need for integrated care models.

Recent advancements in therapeutic modalities offer promising avenues, particularly for treatment-resistant cases. The development of novel agents like aldosterone synthase inhibitors for resistant hypertension, GLP-1 RAs and SGLT2i for T2DM (with their dual cardiorenal benefits), oral PCSK9 inhibitors and RNAi therapies for hyperlipidemia, and targeted biologics and oral BTK inhibitors for severe asthma, signifies a shift towards more personalized and mechanism-specific treatments. In mental health, rapid-acting therapies like ketamine and psychedelic-assisted interventions are transforming the management of severe depression. These innovations hold the potential to significantly improve patient outcomes, reduce disease burden, and enhance quality of life.

In conclusion, effective management of common chronic illnesses in primary care demands a dynamic, evidence-based approach. This includes diligent adherence to evolving guidelines, a strong emphasis on comprehensive lifestyle modifications, proactive screening for and management of comorbidities, and a keen awareness of emerging therapeutic options. The ultimate goal is to empower medical doctors with the knowledge and tools to provide patient-centered care that not only manages symptoms but also fundamentally alters the long-term trajectory of these prevalent

and impactful conditions.

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