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PHARMACOLOGICAL MANAGEMENT OF GRAVES' DISEASE: CURRENT EVIDENCE AND EMERGING THERAPEUTIC TARGETS

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Abstract: Graves' disease represents the most prevalent cause of hyperthyroidism worldwide, affecting approximately 0.5% of the global population. This autoimmune disorder is characterized by the production of thyroid-stimulating hormone receptor antibodies (TRAb) that stimulate excessive thyroid hormone synthesis. Current therapeutic approaches include antithyroid medications, radioactive iodine therapy, and surgical intervention, each presenting distinct advantages and limitations. This comprehensive narrative review examines the pharmacological management landscape of Graves' disease, synthesizing evidence from contemporary clinical studies and treatment guidelines. We explore the mechanisms of action, clinical efficacy, and safety profiles of established treatments including thionamides, beta-adrenergic blockers, and radioiodine. Furthermore, we analyze emerging therapeutic targets such as teprotumumab, rituximab, tocilizumab, TSH receptor-blocking monoclonal antibodies, and small-molecule antagonists that may transform the treatment paradigm. Special considerations for pregnancy, thyroid storm, and refractory cases are also discussed. Understanding these evolving treatment options enables clinicians to deliver individualized, evidence-based care while minimizing adverse outcomes.

Keywords: Graves' disease, hyperthyroidism, antithyroid drugs, methimazole, radioiodine therapy, teprotumumab, TSH receptor, emerging therapies, thyroid eye disease

1. Introduction

Graves' disease stands as the most common etiology of hyperthyroidism in clinical practice, accounting for approximately 60-80% of all cases of excessive thyroid hormone production. This organ-specific autoimmune condition develops when the immune system erroneously produces antibodies that target the thyroid-stimulating hormone receptor (TSHR) on thyroid follicular cells, resulting in unregulated stimulation of thyroid hormone synthesis and secretion. The clinical presentation encompasses a wide spectrum of manifestations ranging from mild thyrotoxicosis to life-threatening thyroid storm, with extrathyroidal complications including Graves' orbitopathy and pretibial myxedema.

The pathogenesis of Graves' disease involves a complex interplay between genetic predisposition and environmental triggers. Susceptibility genes including HLA-DR3, CTLA-4,

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PTPN22, and the TSHR gene itself contribute to disease development. Environmental factors such as iodine excess, stress, smoking, infections, and female sex hormones modulate immune responses, potentially triggering disease onset in genetically susceptible individuals. The female predominance, with a female-to-male ratio of approximately 5-10:1, particularly during the reproductive years, highlights the influence of hormonal factors on disease susceptibility.

The management of Graves' disease has traditionally relied upon three principal therapeutic modalities: antithyroid drugs (ATDs), radioactive iodine (RAI) therapy, and thyroidectomy. Antithyroid medications, including methimazole, carbimazole, and propylthiouracil, function primarily by inhibiting thyroid peroxidase-mediated iodine organification and coupling of iodotyrosines, thereby reducing thyroid hormone synthesis. Radioactive iodine therapy achieves disease control through targeted destruction of thyroid follicular cells, while surgical removal provides definitive treatment with immediate resolution of hyperthyroidism.

Despite the efficacy of these conventional approaches, significant challenges persist. Relapse following ATD discontinuation affects 40-60% of patients after standard 12-18 month courses. Radioactive iodine therapy frequently results in permanent hypothyroidism requiring lifelong hormone replacement, and surgical intervention carries risks including recurrent laryngeal nerve injury and hypoparathyroidism. These limitations have catalyzed intensive research into novel therapeutic strategies targeting the underlying autoimmune mechanisms, including monoclonal antibodies against B-cells, TSH receptor antagonists, and immunomodulatory agents. This review provides a comprehensive analysis of current pharmacological management strategies and examines emerging therapeutic targets that may reshape the treatment landscape for Graves' disease.

2. Pathophysiology and Mechanism of Disease

The central pathophysiological mechanism underlying Graves' disease involves the production of autoantibodies directed against the thyroid-stimulating hormone receptor, termed TSH receptor antibodies or thyrotropin receptor immunoglobulins. The TSH receptor belongs to the G-protein-coupled receptor superfamily, comprising a large extracellular domain responsible for ligand binding, seven transmembrane-spanning domains, and an intracellular signaling domain. Under normal physiological conditions, pituitary-derived TSH binds to this receptor to regulate thyroid hormone production through cyclic adenosine monophosphate (cAMP) signaling pathways.

In Graves' disease, activated B-lymphocytes produce TRAb that mimic TSH action by binding to the TSH receptor extracellular domain. These stimulating autoantibodies activate adenylyl cyclase, leading to increased intracellular cAMP levels and subsequent upregulation of thyroid hormone synthesis. Unlike TSH, which is subject to negative feedback regulation by circulating thyroid hormones, TRAb production occurs without such regulatory constraints, resulting in persistent, uncontrolled thyroid stimulation. This explains the characteristic diffuse goiter and biochemical hyperthyroidism observed in affected patients.

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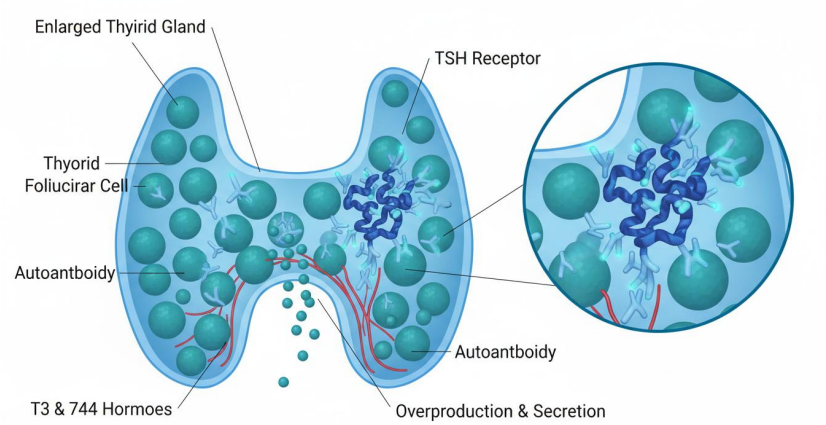

Figure 1: Pathophysiology of Graves' disease showing TSH receptor stimulation by autoantibodies and subsequent thyroid hormone overproduction.

The extrathyroidal manifestations of Graves' disease, particularly Graves' orbitopathy, involve related pathophysiological processes. Orbital fibroblasts express functional TSH receptors, and their stimulation by circulating TRAb promotes the production of glycosaminoglycans including hyaluronic acid, leading to tissue expansion within the confined orbital space. Additionally, the insulin-like growth factor-1 receptor (IGF-1R) forms functional complexes with TSH receptors on orbital fibroblasts, B-cells, and T-cells, contributing to inflammatory responses and adipogenesis. This TSHR-IGF-1R interaction has emerged as a critical therapeutic target, forming the mechanistic basis for teprotumumab therapy in thyroid eye disease.

Table 1: Classification and Characteristics of TSH Receptor Antibodies

Antibody Type	Mechanism of Action	Clinical Significance
TSHR-Stimulating Antibodies	Activate TSH receptor, increase cAMP, stimulate hormone synthesis	Cause hyperthyroidism; correlate with disease severity
TSHR-Blocking Antibodies	Antagonize TSH receptor, inhibit receptor signaling	May cause hypothyroidism; can coexist with stimulating antibodies
TSHR-Neutral Antibodies	Bind receptor without activating or blocking	Clinical significance unclear; may modulate immune response

3. Current Pharmacological Management

3.1 Antithyroid Drugs (Thionamides)

Thionamides remain the cornerstone of pharmacological management for Graves' hyperthyroidism worldwide. The three agents available for clinical use include methimazole (MMI), its prodrug carbimazole (CBZ), and propylthiouracil (PTU). These medications are actively transported into thyroid follicular cells where they exert their primary pharmacological

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effects through inhibition of thyroid peroxidase, the enzyme responsible for both iodine organification and the coupling of iodotyrosine residues to form thyroid hormones.

Methimazole has emerged as the preferred first-line agent for most adult patients due to its favorable pharmacokinetic profile and reduced risk of serious adverse events compared to PTU. With a plasma half-life of approximately 6-8 hours, MMI can be administered once or twice daily, enhancing patient adherence. The drug demonstrates 10-fold greater potency than PTU on a milligram basis and achieves euthyroidism more rapidly. Current guidelines recommend initial doses of 10-30 mg daily depending on disease severity, with titration to maintenance doses of 5-10 mg once biochemical control is achieved. The block-replace regimen, utilizing higher MMI doses combined with levothyroxine replacement, offers the advantage of fewer monitoring visits but is associated with a higher incidence of adverse effects.

Propylthiouracil retains an important but more limited role in contemporary practice. Its distinct mechanism of partially inhibiting peripheral conversion of thyroxine (T4) to triiodothyronine (T3) through 5'-deiodinase inhibition provides theoretical advantages in severe thyrotoxicosis. However, the FDA boxed warning regarding severe liver injury, including fulminant hepatic failure requiring transplantation, has significantly restricted PTU use. PTU is currently reserved for first-trimester pregnancy (due to the teratogenic risk of methimazole embryopathy), thyroid storm management, and cases of severe methimazole intolerance or allergy.

The optimal duration of ATD therapy remains a subject of ongoing investigation. Traditional 12-18 month treatment courses achieve remission in approximately 30-55% of patients, with relapse commonly occurring within the first year following discontinuation. Emerging evidence from prospective studies suggests that extended treatment durations significantly improve remission rates. A landmark randomized clinical trial demonstrated that 60-120 months of continuous MMI therapy achieved remission in approximately 84% of patients, compared to 47% with conventional duration therapy. Long-term low-dose MMI maintenance (2.5-5 mg daily) has proven safe and effective, with minimal adverse effects over treatment periods exceeding 10 years.

Table 2: Comparison of Antithyroid Drug Therapies

Parameter	Methimazole	Propylthiouracil (PTU)	Carbimazole
Mechanism	Inhibits TPO; blocks iodine organification	Inhibits TPO; blocks peripheral T4-to-T3 conversion	Prodrug of methimazole
Potency	10x more potent than PTU	Less potent; requires higher doses	Equivalent to methimazole
Typical Dose	10-30 mg daily initially; 5-10 mg maintenance	100-150 mg every 8 hours	15-40 mg daily initially
Administration	Once daily (long half-life)	Every 6-8 hours (short half-life)	Once or twice daily
Major Adverse	Agranulocytosis	Agranulocytosis,	Similar to

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Parameter	Methimazole	Propylthiouracil (PTU)	Carbimazole
Effects	(0.3%), hepatotoxicity (cholestatic)	severe hepatotoxicity (boxed warning)	methimazole
Preferred Indications	First-line for most adults	First trimester pregnancy, thyroid storm, MMI allergy	Alternative to MMI in some regions

3.2 Beta-Adrenergic Blockers

Beta-adrenergic antagonists play an essential adjunctive role in the symptomatic management of Graves' hyperthyroidism. These agents do not directly alter thyroid hormone synthesis or secretion but rather antagonize the increased beta-adrenergic receptor expression and sensitivity induced by excess thyroid hormones. Clinical benefits include reduction of tachycardia, tremor, anxiety, heat intolerance, and muscle weakness. Propranolol, a non-selective beta-blocker, has been most extensively studied and offers the additional advantage of inhibiting peripheral T4-to-T3 conversion at higher doses, though this effect is quantitatively modest.

Current recommendations advocate beta-blocker initiation at the time of Graves' disease diagnosis, particularly in symptomatic patients or those with significant cardiovascular manifestations. Propranolol is typically initiated at 20-40 mg orally every 6-8 hours and titrated based on clinical response. Selective beta-1 antagonists such as atenolol and metoprolol may be preferred in patients with reactive airway disease where non-selective blockade could precipitate bronchospasm. In acute settings, intravenous esmolol, with its ultra-short half-life of approximately 9 minutes, provides rapid titration for hemodynamically unstable patients and represents the preferred agent in thyroid storm or perioperative management.

3.3 Radioactive Iodine Therapy

Radioactive iodine-131 (I-131) therapy has been utilized for over seven decades as a definitive treatment for Graves' hyperthyroidism. The therapeutic mechanism involves selective uptake of radioactive iodine by thyroid follicular cells, with subsequent beta-particle emission causing targeted cellular destruction and glandular ablation. This approach effectively eliminates hyperthyroidism in the majority of patients, with success rates of 75-90% following a single treatment dose.

Patient preparation for RAI therapy includes discontinuation of ATDs 3-7 days before administration to optimize iodine uptake, though recent evidence suggests concurrent ATD use may not significantly compromise outcomes while reducing the risk of transient thyroid hormone exacerbation. Various dosing strategies exist, including fixed-dose approaches (typically 10-15 mCi), thyroid weight-based calculations, and dosimetric methods targeting specific radiation doses to the gland. Higher doses correlate with increased success rates but also higher rates of permanent hypothyroidism requiring lifelong levothyroxine replacement.

Special considerations apply to patients with Graves' orbitopathy undergoing RAI therapy. Radioactive iodine administration may exacerbate active eye disease in approximately 15-20% of patients with pre-existing orbitopathy. Current guidelines recommend prophylactic corticosteroid coverage (prednisone 0.3-0.5 mg/kg daily tapered over 3 months) for patients with moderate-to-severe active orbitopathy receiving RAI therapy. Patients with smoking history

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require particular attention, as tobacco use significantly increases the risk of orbitopathy progression following radioactive iodine treatment.

4. Surgical Management

Thyroidectomy represents a definitive treatment option for Graves' disease, offering the advantage of immediate and permanent resolution of hyperthyroidism while avoiding the risks of prolonged medication use or radiation exposure. Total or near-total thyroidectomy is the preferred surgical approach, as subtotal resection carries unacceptably high recurrence rates of 10-30%. Recent comparative effectiveness research suggests that patients receiving surgery as initial treatment may experience lower long-term all-cause mortality and reduced relapse rates compared to those treated with ATDs or RAI.

Surgical indications include large goiters with compressive symptoms, suspicion of thyroid malignancy (notably, concomitant thyroid cancer is identified in 5-15% of surgical specimens from Graves' disease patients), moderate-to-severe active orbitopathy, pregnancy with failure of ATD therapy, and patient preference for rapid definitive treatment. Preoperative preparation requires achieving euthyroidism through ATD therapy, typically supplemented with iodine preparations (Lugol's solution or potassium iodide) for 10-14 days preoperatively to reduce thyroid vascularity and operative bleeding.

Complication rates at experienced high-volume centers are acceptably low. A large retrospective study reported transient recurrent laryngeal nerve palsy in 6.9% of patients, with permanent injury occurring in 1.4%. Transient hypoparathyroidism occurred in 19.4% of patients following total thyroidectomy, with permanent hypoparathyroidism in 1.4%. The use of intraoperative nerve monitoring and prophylactic calcium supplementation has contributed to reducing these complication rates. All patients require lifelong levothyroxine replacement following total thyroidectomy, necessitating careful dose titration and long-term monitoring.

5. Emerging Pharmacological Therapies

The evolving understanding of Graves' disease immunopathogenesis has catalyzed development of targeted biologic therapies that address the underlying autoimmune mechanisms rather than merely controlling thyroid hormone production. These novel agents represent a paradigm shift toward disease-modifying treatment approaches with the potential to induce durable remission while preserving thyroid function.

5.1 Teprotumumab

Teprotumumab, a fully human monoclonal antibody targeting the insulin-like growth factor-1 receptor (IGF-1R), represents the most significant therapeutic advance in Graves' orbitopathy management in decades. Approved by the FDA in 2020 for active thyroid eye disease, teprotumumab blocks the functional complex formed between IGF-1R and TSH receptor on orbital fibroblasts, B-cells, and T-cells, thereby attenuating the inflammatory cascade and tissue remodeling characteristic of Graves' orbitopathy.

The OPTIC phase 3 clinical trial demonstrated remarkable efficacy, with 83% of teprotumumab-treated patients achieving the primary endpoint of proptosis reduction greater than or equal to 2 mm compared to 10% in the placebo group. Significant improvements were also observed in clinical activity score, diplopia, and quality of life measures. Treatment consists

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of eight intravenous infusions (10 mg/kg initial dose, 20 mg/kg subsequent doses) delivered every three weeks. Common adverse effects include hyperglycemia, hearing impairment including hearing loss, muscle spasms, nausea, and infusion reactions. The potential for permanent hearing loss necessitates audiometric monitoring during treatment.

5.2 Rituximab

Rituximab, a chimeric monoclonal antibody targeting the CD20 antigen expressed on pre-B and mature B-lymphocytes, has been investigated for both Graves' hyperthyroidism and orbitopathy. By depleting B-cells, rituximab reduces the production of pathogenic autoantibodies including TRAb. Early studies demonstrated variable effects on hyperthyroidism control, with some trials showing reduction in TRAb levels without significant impact on thyroid function, while others suggested prolonged remission in patients with mild disease.

The RIGD multicenter phase 2 trial evaluated rituximab in 27 young patients (ages 12-20 years) with Graves' disease, administering a single 500 mg dose combined with ATDs for 12 months. At two-year follow-up, 48% of patients achieved remission, suggesting potential benefit when combined with conventional therapy. Rituximab appears most effective in patients with lower baseline TRAb levels (less than 5 IU/L). For Graves' orbitopathy, evidence from randomized controlled trials has yielded inconsistent results, and rituximab is currently reserved for corticosteroid-refractory cases or as a second-line immunosuppressive agent. Safety considerations include infusion reactions, increased infection risk, and rare but serious adverse events including progressive multifocal leukoencephalopathy.

5.3 Tocilizumab

Tocilizumab, a humanized monoclonal antibody targeting the interleukin-6 (IL-6) receptor, has demonstrated promising efficacy in moderate-to-severe Graves' orbitopathy refractory to conventional corticosteroid therapy. IL-6, a pleiotropic cytokine elevated in active orbitopathy, plays a central role in orbital inflammation through activation of T-helper cells, B-cell differentiation, and stimulation of glycosaminoglycan production by orbital fibroblasts. By blocking IL-6 signaling, tocilizumab interrupts multiple pathogenic pathways simultaneously.

Clinical experience with tocilizumab in glucocorticoid-refractory Graves' orbitopathy has shown significant reduction in clinical activity scores and improvement in ocular parameters. A retrospective series of 48 patients with severe refractory orbitopathy demonstrated rapid and sustained improvements in best-corrected visual acuity, clinical activity score, and intraocular pressure following tocilizumab therapy at 8 mg/kg intravenously every four weeks. Notably, a decrease in thyroid-stimulating immunoglobulin levels was observed, suggesting an upstream immunomodulatory effect. No severe adverse events were reported in this cohort, establishing tocilizumab as a well-tolerated steroid-sparing alternative.

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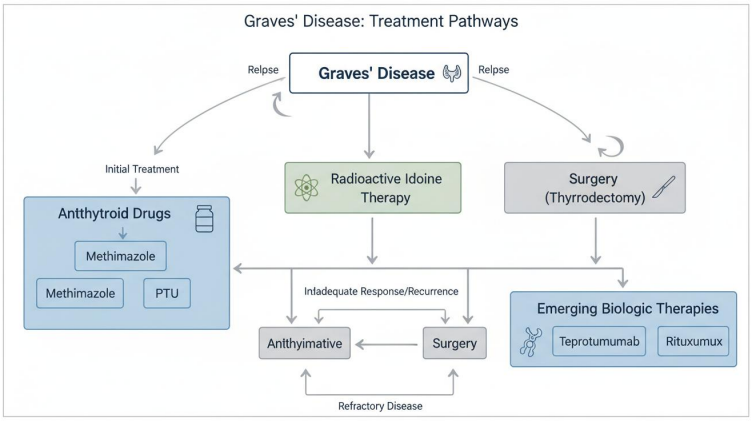

Figure 2: Overview of current and emerging treatment pathways for Graves' disease management.

5.4 TSH Receptor-Blocking Monoclonal Antibodies

The development of monoclonal antibodies that specifically block TSH receptor activation represents a direct therapeutic approach to Graves' disease pathophysiology. K1-70, a human monoclonal TSH receptor autoantibody with blocking activity, has been evaluated in phase 1 clinical trials. This antibody binds the TSH receptor with high affinity (Kd approximately 4 x 10^10 mol/L), preventing stimulation by both endogenous TSH and pathogenic TRAb.

In the first-in-human study, K1-70 administration to patients with stable Graves' disease on ATD therapy resulted in dose-dependent TSH elevation and transition to hypothyroidism in 67% of subjects overall, and 100% of those receiving higher doses (50-150 mg). Importantly, K1-70 was well tolerated with minimal adverse events and no significant immunogenic responses. The ability to achieve rapid biochemical control while potentially preserving thyroid function represents a significant theoretical advantage over ablative therapies. Further clinical trials are needed to establish optimal dosing regimens and long-term efficacy.

5.5 Small-Molecule TSH Receptor Antagonists

Small-molecule ligands that function as inverse agonists or neutral antagonists of the TSH receptor represent another promising therapeutic direction. These compounds bind to allosteric sites within the transmembrane domain of TSHR, distinct from the extracellular antibody-binding region, thereby inhibiting both basal and agonist-induced receptor signaling. Lead compounds including ANTAG-3, VA-K-14, and S37 have demonstrated efficacy in preclinical models.

ANTAG-3 administration in mouse models of Graves' disease achieved a 44% reduction in serum free T4 levels and significantly decreased expression of thyroid-specific genes including sodium-iodide symporter and thyroperodixase. VA-K-14 effectively inhibited TSHR stimulation induced by sera from patients with active Graves' disease. The potential for oral administration, structural stability, and lack of immunogenicity make small-molecule antagonists particularly attractive candidates for clinical development. However, challenges remain regarding the structural homology between TSHR and other glycoprotein hormone receptors (follicle-stimulating hormone receptor, luteinizing hormone receptor), necessitating careful optimization to avoid off-target reproductive effects.

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Table 3: Summary of Emerging Pharmacological Therapies for Graves' Disease

Agent	Target	Mechanism	Development Stage
Teprotumumab	IGF-1 Receptor	Blocks TSHR-IGF-1R complex, reduces inflammation and fibrosis	FDA-approved for TED (2020)
Rituximab	CD20 on B-cells	B-cell depletion, reduces autoantibody production	Phase 2 trials for GD
Tocilizumab	IL-6 Receptor	Blocks IL-6 signaling, anti-inflammatory	Clinical use for refractory GO
K1-70	TSH Receptor	Competitive antagonist, blocks receptor activation	Phase 1 completed
ANTAG-3, VA-K-14	TSH Receptor (allosteric)	Small-molecule inverse agonists	Preclinical development
Batoclimab	Neonatal Fc Receptor	Enhances autoantibody clearance including TRAb	Phase 2 trials ongoing

6. Special Clinical Considerations

6.1 Pregnancy

The management of Graves' disease during pregnancy requires careful balancing of maternal thyroid control with fetal safety. Untreated maternal hyperthyroidism increases risks of spontaneous abortion, preterm delivery, preeclampsia, and fetal growth restriction. Both ATDs cross the placenta and can cause fetal hypothyroidism if doses are excessive, necessitating use of the lowest effective dose to maintain maternal free T4 at the upper limit of the pregnancy-specific reference range.

Current guidelines recommend PTU during the first trimester due to the teratogenic risks associated with methimazole, including aplasia cutis and choanal/esophageal atresia, though the absolute risk is low (approximately 2-4% versus 1.5% background). Transition to methimazole is recommended at the beginning of the second trimester due to the risk of PTU-associated hepatotoxicity. TRAb levels should be measured in the third trimester, as levels exceeding 3 times the upper limit of normal predict increased risk of fetal or neonatal Graves' disease caused by transplacental antibody transfer.

6.2 Thyroid Storm

Thyroid storm constitutes a life-threatening emergency requiring immediate, aggressive multimodal therapy in an intensive care setting. This condition, characterized by severe thyrotoxicosis with multi-organ decompensation, carries mortality rates of 10-30% even with

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optimal treatment. The therapeutic approach follows a structured protocol targeting multiple points in thyroid hormone synthesis, release, and peripheral action.

The BB-SIT mnemonic provides a framework for emergency management: Beta-blockade (typically propranolol or esmolol for rate control), Block synthesis with thionamides (methimazole 60-80 mg daily or PTU 600-1000 mg loading dose followed by 200-250 mg every 4 hours), inhibit hormone release with Sodium iodide or Lugol's solution (administered at least one hour after thionamides to prevent utilization as substrate for new hormone synthesis), and prevent peripheral T4-to-T3 conversion with hydrocortisone (100 mg intravenously every 8 hours). Identification and treatment of precipitating factors including infection, surgery, trauma, or iodine exposure is essential. Supportive measures include aggressive fluid resuscitation, cooling blankets, and management of potential cardiovascular collapse.

7. Conclusion

The pharmacological management of Graves' disease continues to evolve, with expanding therapeutic options offering opportunities for individualized patient care. Conventional treatments including thionamides, radioactive iodine, and surgery remain effective for the majority of patients, with methimazole established as the first-line pharmacological agent due to its efficacy and favorable safety profile. Evidence supporting extended-duration ATD therapy achieving remission rates exceeding 80% challenges the traditional paradigm of limited treatment courses followed by expectant monitoring.

The emergence of targeted biologic therapies represents the most significant development in Graves' disease management in recent years. Teprotumumab has transformed the treatment landscape for moderate-to-severe Graves' orbitopathy, while rituximab and tocilizumab provide valuable options for refractory cases. Novel approaches including TSH receptor-blocking monoclonal antibodies and small-molecule antagonists offer the promise of disease-modifying therapy that targets the underlying autoimmune mechanism rather than merely controlling hormone production.

Future directions in Graves' disease pharmacotherapy should focus on several key areas: validation of optimal treatment algorithms incorporating patient-specific risk factors; establishment of biomarkers to predict treatment response and relapse; development of combination strategies integrating conventional and biologic agents; and continued refinement of targeted immunotherapies. The ultimate goal remains the development of treatments that induce durable remission while preserving thyroid function and minimizing treatment-related morbidity. As our understanding of Graves' disease immunopathogenesis continues to advance, the prospects for achieving this goal have never been more promising.

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