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Review Article

Emerging insights into the use of dexamethasone for high-altitude illness: bridging basic pharmacology and clinical practice

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ABSTRACT

Acute mountain sickness (AMS) and its severe forms high-altitude cerebral edema (HACE) and high-altitude pulmonary edema (HAPE) result from hypobaric hypoxia that triggers vascular leak, inflammation, and metabolic stress. Among preventive agents, acetazolamide remains conventional, but dexamethasone has emerged as the most potent pharmacologic safeguard due to its rapid and multi-level protective mechanisms. Acting through both genomic and non-genomic pathways, dexamethasone suppresses NF-κB and HIF-1α signalling, reinforces endothelial barrier integrity, reduces cytokine-driven edema, and enhances mitochondrial energy efficiency, collectively restoring vascular and metabolic stability under hypoxic stress. Evidence from randomized trials and meta-analyses demonstrates a 60-70% reduction in AMS incidence and accelerated recovery in HACE and HAPE with dexamethasone therapy. Multi-omics analyses further reveal that the drug reprograms over a thousand genes involved in immune, oxidative, and metabolic regulation, underscoring its system-wide impact. Recent advances including inhaled, transdermal, and depot formulations, as well as pharmacogenomic-guided dosing are transforming dexamethasone from a symptom-relief drug to a precision altitude pharmacology agent. Its unmatched combination of anti-inflammatory, anti-edematous, and metabolic-stabilizing actions firmly establishes dexamethasone as the most comprehensive and mechanistically validated therapy for both prevention and treatment of high-altitude illness.

Keywords: Dexamethasone, Acute mountain sickness, High-altitude cerebral edema, High-Altitude Pulmonary Edema, Glucocorticoid receptor, Hypoxia-inducible factor

INTRODUCTION

Acute mountain sickness (AMS) represents the earliest and most common manifestation of high-altitude illness that arises when unacclimatized individuals ascend rapidly to elevations usually above 2,500 m. It is characterized by headache, dizziness, anorexia, nausea, fatigue, and sleep disturbance within 6-24 hours of arrival at altitude. In susceptible persons, AMS may progress to HACE and HAPE, both of which can be life-threatening if not recognized and treated promptly.[1,2]

The physiological challenge underlying AMS is hypobaric hypoxia the reduced partial pressure of inspired oxygen that diminishes arterial oxygen saturation and compromises tissue oxygen delivery. The brain and lungs, being highly oxygen-dependent organs, are especially vulnerable.[1] Although most individuals acclimatize via ventilatory and hematologic adjustments, rapid ascent disturbs oxygen balance, predisposing to altitude illness. While gradual ascent remains ideal, it is impractical for climbers, trekkers, rescue teams, and military personnel, making pharmacologic prophylaxis essential. Acetazolamide, the standard carbonic anhydrase inhibitor,

improves ventilation by inducing mild acidosis, whereas dexamethasone a potent synthetic glucocorticoid offers rapid, well-tolerated protection where acetazolamide is unsuitable. Its proven efficacy and broad molecular actions make it pivotal in altitude medicine.

Historically, "mountain sickness" was noted by 19th-century explorers, and mid-20th-century studies identified hypoxia-driven hyperventilation, sympathetic activation, and altered cerebral blood flow as key mechanisms.[3]

By the 1970s-1980s, controlled trials established acetazolamide as an effective preventive agent, shifting focus toward corticosteroids. Dexamethasone, with high glucocorticoid potency and negligible mineralocorticoid activity, was soon recognized for its rapid efficacy in relieving severe AMS and HACE.

PATHOPHYSIOLOGY OF AMS

AMS results from hypoxia-induced vascular and inflammatory responses. Reduced ambient oxygen activates carotid chemoreceptors, increasing ventilation yet causing alkalosis; inadequate compensation leads to cerebral hypoxemia, vasodilation, and capillary leakage.[4]

Cerebral mechanisms

The most accepted model of AMS pathogenesis centers on vasogenic cerebral edema. Hypoxia induces endothelial dysfunction and disrupts the blood-brain barrier through up-regulation of vascular endothelial growth factor (VEGF), nitric oxide, as well as the inflammatory cytokines.[3,5]

The consequent leakage of plasma proteins and fluid into the interstitial space elevates intracranial pressure and manifests as headache and dizziness. Magnetic-resonance studies demonstrate mild brain swelling even in uncomplicated AMS cases.[6]

Dexamethasone counters these effects by reducing endothelial permeability, inhibiting VEGF expression, and stabilizing astrocyte function. These vascular and cellular mechanisms explain the rapid symptom improvement observed in treated individuals.

Pulmonary mechanisms

Although AMS primarily affects the brain, hypoxia-induced pulmonary vasoconstriction can cause capillary stress failure and interstitial edema. Resulting fluid accumulation impairs gas exchange, intensifying hypoxemia and cerebral symptoms.

Glucocorticoids counter this by enhancing alveolar sodium and water reabsorption via epithelial sodium channels and Na^+/K^+-ATPase activity, thereby preventing alveolar flooding and maintaining oxygenation.[7]

Inflammatory pathways

Emerging evidence implicates systemic inflammation as a unifying mechanism linking cerebral and pulmonary responses.[8] Hypoxia activates transcription factors such as hypoxia-inducible factor-1α (HIF-1α) and nuclear factor-κB (NF-κB), promoting cytokine release (IL-1β, IL-6, TNF-α). These mediators amplify endothelial permeability and leukocyte adhesion. Dexamethasone exerts broad anti-inflammatory control by suppressing NF-κB signaling, up-regulating anti-inflammatory genes (annexin A1, IL-10), and reducing leukocyte migration.[9-11]

Genetic and individual susceptibility

Not all individuals develop AMS under identical hypoxic exposure. Genetic polymorphisms in HIF-pathway genes, endothelial nitric-oxide synthase, and cytokine promoters contribute to variability in susceptibility.[12]

Epigenetic modulation and prior acclimatization also influence outcomes. Understanding this heterogeneity underscores why dexamethasone's transcriptomic modulation of immune and metabolic genes may yield individualized protective responses.[13]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The Lake Louise scoring system (LLSS) provides a standardized diagnostic framework for AMS. It combines self-reported symptoms-headache, gastrointestinal upset, fatigue, dizziness, and sleep difficulty-with clinical signs such as tachycardia or mild peripheral edema.[14,15] A total score ≥ 3 with headache is diagnostic.

AMS typically appears after 6-10 hours of ascent and peaks within 24–48 hours.[16] Most cases are mild, but progression to HACE manifests as ataxia, altered consciousness, or focal neurologic deficits. Pulmonary involvement (HAPE) presents with cough, dyspnea, and crackles.

Early recognition is critical because symptoms can be subtle and subjective. Routine monitoring of oxygen saturation and periodic assessment using LLSS aid timely intervention and standard management (Table 1).

Dexamethasone is particularly effective when administered at the onset of moderate symptoms, often producing perceptible improvement within 6-12 hours.

This Table 1 summarizes the principal pharmacologic agents currently used for prophylaxis and treatment of AMS. It contrasts their mechanisms, dosing schedules, onset of action, and safety profiles, thereby setting the clinical context for understanding the distinct mechanistic and therapeutic advantages of dexamethasone, which are discussed in the subsequent sections.

Table 1: Comparative overview of pharmacologic agents used in the prevention and management of AMS.

Drug	Mechanism	Dosage	Onset of action	Advantage	Best use scenario
Dexamethasone	Potent glucocorticoid; inhibits NF-κB, VEGF, and HIF-1α; stabilizes BBB	4 mg PO q12h (prophylaxis); 8 mg IV/IM → 4 mg q6h (treatment)	Rapid (2-6 h)	Rapid relief, CNS protection, effective for HACE	Rapid ascent, HACE rescue, military or emergency deployment
Acetazolamide	Carbonic-anhydrase inhibitor; induces metabolic acidosis → ↑ ventilation	125-250 mg PO BID	Moderate (12-24 h)	Proven preventive efficacy, minimal systemic toxicity	Gradual ascent prophylaxis, long expeditions
Nifedipine	Calcium-channel blocker; ↓ pulmonary arterial pressure	20 mg SR PO q8h	1-3 h	Prevents / treats HAPE	HAPE prophylaxis or adjunct therapy
Budesonide (Inhaled)	Corticosteroid acting locally in lung; ↓ alveolar inflammation	200 µg BID inhaled	3-6 h	Fewer systemic effects, easy field use	Alternative for HAPE risk or steroid-sensitive individuals
Ibuprofen	Non-steroidal anti-inflammatory; prostaglandin inhibition	600 mg PO q8h	1-2 h	Over-the-counter, reduces headache score	Mild AMS symptom management

RATIONALE FOR USING DEXAMETHASONE

Dexamethasone prevents and treats AMS through multiple complementary actions: it rapidly crosses the blood-brain barrier to achieve high CNS levels, inhibits prostaglandin synthesis to reverse vasogenic edema, enhances ventilatory drive by increasing chemoreceptor sensitivity to CO_2, and suppresses cytokine release to limit hypoxic inflammation. These combined effects differ from acetazolamide, which primarily acts via metabolic acidosis and ventilatory stimulation, making dexamethasone especially valuable for rapid ascent, field rescue, and high-altitude flight scenarios.[17,18] Dexamethasone is a synthetic fluorinated corticosteroid derived from prednisolone, possessing high glucocorticoid potency (approximately 25-30 times that of hydrocortisone) and negligible mineralocorticoid activity. This structural modification allows powerful anti-inflammatory and immunosuppressive actions while minimizing sodium retention and fluid overload advantages particularly valuable in altitude illness where cerebral or pulmonary edema are key pathologies.[19] The drug exhibits excellent oral bioavailability, a long plasma half-life of 36-54 hours, and substantial tissue penetration, including ready passage across the blood–brain barrier. After absorption, it binds weakly to plasma proteins, ensuring a large free fraction available for biological activity. Hepatic metabolism is predominantly via CYP3A4, and inactive metabolites are excreted renally.[20] These pharmacokinetic features provide sustained plasma concentrations during ascent phases when repeated dosing might be logistically difficult.[16]

Molecular basis of action

Glucocorticoid receptor binding and genomic effects

Dexamethasone acts through the glucocorticoid receptor (GR), a ligand-activated transcription factor belonging to the nuclear receptor superfamily. Upon binding, the receptor-ligand complex translocates to the nucleus, where it influences gene expression through two main mechanisms. In Trans-activation binding to glucocorticoid response elements (GREs) on DNA, up-regulating anti-inflammatory proteins such as lipocortin-1 (annexin A1), secretory leukocyte protease inhibitor, and IL-10.[21] In Trans-repression interference with transcription factors such as NF-κB and AP-1, thereby down-regulating genes encoding cytokines (IL-1β, IL-6, TNF-α), chemokines, adhesion molecules, and enzymes like COX-2.[22] Through these processes, dexamethasone modulates hundreds of genes involved in immune cell differentiation, endothelial stability, and oxidative stress response (Figure 1).[23]

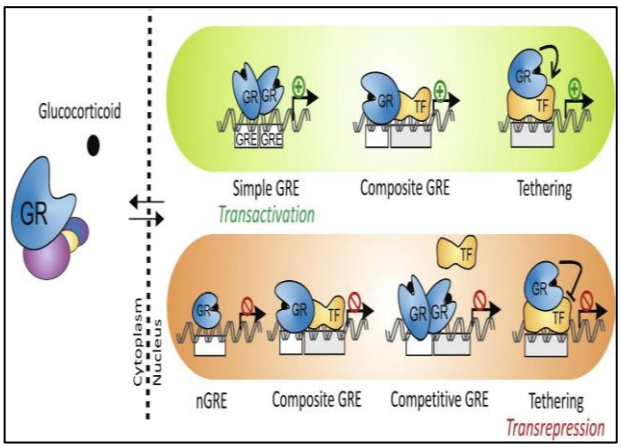

Figure 1: Mechanisms of glucocorticoid receptor–mediated gene regulation: transactivation and transrepression pathways.[23]

Non-genomic mechanisms

Beyond genomic regulation, dexamethasone also produces rapid non-genomic effects by modulating membrane glucocorticoid receptors and stabilizing cell membranes. These actions limit calcium influx, reduce mast-cell degranulation, and decrease vascular permeability, thereby

preserving microcirculatory integrity and preventing early vasogenic edema at altitude.[18,24] Recent structural studies have refined our understanding of glucocorticoid receptor (GR) isoforms and their tissue-specific signaling in hypoxic conditions. Dexamethasone primarily binds to GR-α, the transcriptionally active form, initiating DNA-dependent regulation of hundreds of hypoxia-responsive genes.[25] However, alternate splicing produces GR-β, which acts as a dominant inhibitor and may explain inter-individual differences in AMS susceptibility.[26] Phosphoproteomic analyses show that dexamethasone induces Ser211 phosphorylation of GR, enhancing its nuclear localization and interaction with co-repressors such as NCoR and SMRT.[27] This epigenomic modulation limits pro-inflammatory transcription of IL-1β, COX-2, and VEGF-A during altitude hypoxia.[28] In neural tissue, GR activation directly up-regulates aquaporin-4 suppressor genes, thereby preserving astrocytic integrity and preventing cytotoxic edema. Animal experiments demonstrate that dexamethasone's protective profile correlates with up-regulation of 11β-hydroxysteroid dehydrogenase-1 (11β-HSD1) in the hippocampus and lung, which regenerates active cortisol equivalents under stress, amplifying local anti-inflammatory defense.[29]

Studies on blood–brain barrier transport kinetics reveal high lipophilicity (logP ≈1.8) and efficient P-glycoprotein evasion, accounting for rapid CNS penetration and symptom reversal in AMS.[30] Collectively, these findings extend the pharmacologic rationale of dexamethasone from mere cytokine suppression to a precision molecular orchestrator of neurovascular stability.

Anti-inflammatory and anti-edematous actions in AMS

Suppression of cytokine storm

During hypoxic stress, immune cells release pro-inflammatory cytokines that compromise vascular function. Dexamethasone effectively interrupts this cascade. Transcriptomic profiling of peripheral blood mononuclear cells (PBMCs) at altitude revealed marked down-regulation of genes encoding IL-6, IL-8, CCL2, and TNF-α after dexamethasone prophylaxis.[31] This suppression correlates with improved oxygen saturation and reduced AMS symptom scores. The reduction in circulating inflammatory mediators also limits activation of microglia and astrocytes within the central nervous system, further protecting against cerebral dysfunction.[32,33]

Inhibition of endothelial activation

Hypoxia increases endothelial adhesion molecules (ICAM-1, VCAM-1), promoting leukocyte attachment linked to AMS severity. Dexamethasone counteracts this by down-regulating adhesion molecules and up-regulating tight-junction proteins (claudin-5, occludin), thereby preserving blood-brain barrier integrity and limiting capillary leakage.[34]

Regulation of vascular permeability factors

Experimental models show that dexamethasone inhibits vascular endothelial growth factor (VEGF) and endothelin-1 production two potent mediators of hypoxia-induced permeability and vasoconstriction.[3,35] By balancing vasodilatory and vasoconstrictive forces, it normalizes cerebral perfusion pressure and prevents excessive intracranial fluid accumulation.

Modulation of oxidative stress

Hypoxia elevates reactive oxygen species, causing lipid peroxidation and mitochondrial injury. Dexamethasone up-regulates antioxidant enzymes (superoxide dismutase, glutathione peroxidase) and inhibits NADPH oxidase, thereby reducing oxidative damage to endothelial and neuronal cells.[36]

Pulmonary and cerebral protective effects

Pulmonary effects

Dexamethasone acts on alveolar epithelial cells to promote sodium and water clearance from alveolar spaces. It up-regulates the epithelial sodium channel (ENaC) and Na^+/K^+-ATPase, improving alveolar fluid reabsorption. Additionally, it stimulates surfactant production, which reduces surface tension and maintains alveolar stability. These effects are pivotal in preventing or attenuating HAPE that may accompany AMS (Figure 2).[37]

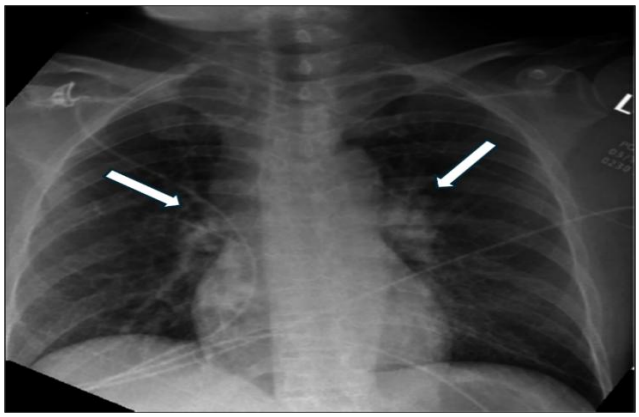

Figure 2: Chest radiograph findings consistent with HAPE.

An anteroposterior chest radiograph shows diffuse pulmonary vascular congestion (depicted by white arrows) without cardiomegaly or consolidation, consistent with early HAPE. The findings reflect increased vascular permeability, which dexamethasone counteracts by stabilizing endothelium and suppressing inflammation (Figure 2).[38] Furthermore, dexamethasone suppresses pulmonary vascular inflammation by inhibiting the expression of endothelin-1 and phospholipase A_2, leading to decreased pulmonary arterial pressure and improved ventilation-perfusion matching.[18,39]

Cerebral effects

In the central nervous system, dexamethasone stabilizes astrocyte end-feet and enhances expression of aquaporin-4 channels, facilitating regulated water transport and preventing cytotoxic edema. Functional MRI studies suggest that dexamethasone reduces cerebral blood-flow fluctuations under hypoxia, maintaining oxygen delivery without excessive vasodilation.[15] These findings corroborate the clinical observation of rapid headache relief and improved coordination in treated climbers.

The characteristic radiologic changes of HACE diffuse vasogenic edema and micro-hemorrhages in subcortical and callosal regions are illustrated in Figures 4 and 5. These images exemplify the pathophysiological substrate upon which dexamethasone exerts its neuroprotective and anti-edematous actions, reinforcing the clinical relevance of corticosteroid therapy in AMS.

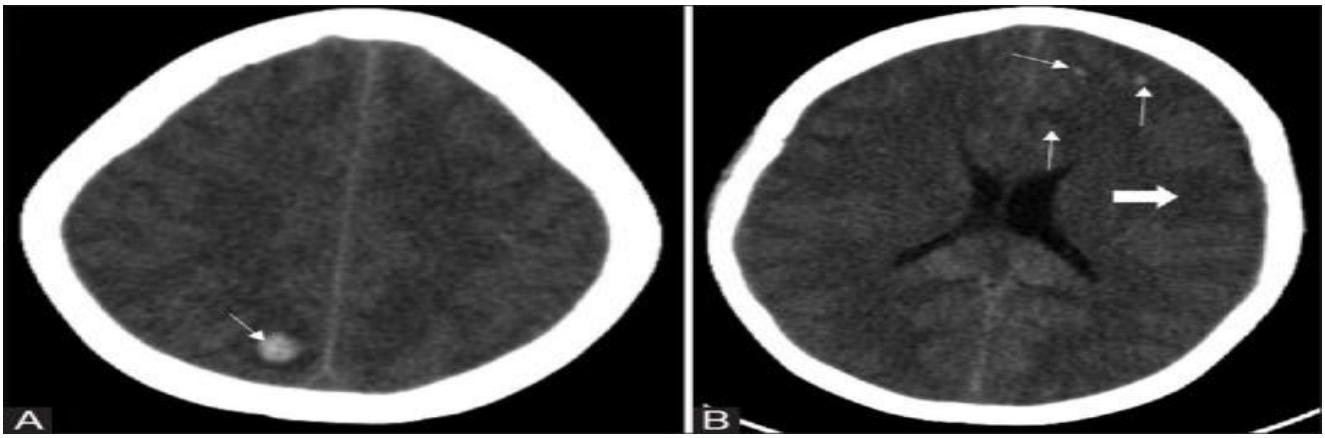

Figure 3 (A and B): Neuroimaging evidence of hemorrhagic and edematous lesions in HACE.

*Non-contrast CT (NCCT) scans show multiple punctate cortical and subcortical hemorrhagic foci in the right parietal (A) and left frontal lobes (B) (thin arrows). Note the associated subcortical edema in the left frontal lobe (solid arrow, B), reflecting vasogenic injury typical of HACE (Figure 3).[40]

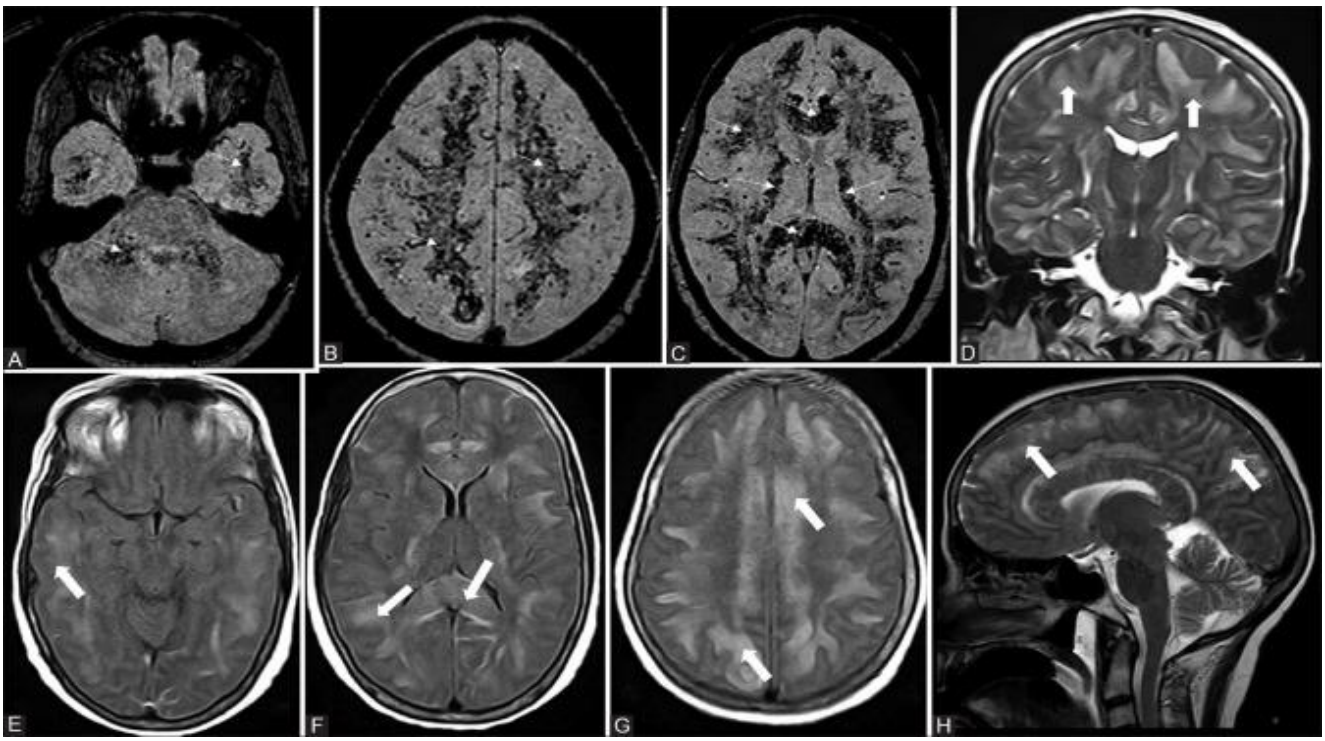

Figure 4 (A-H): MRI demonstration of diffuse microhemorrhages and white-matter edema in severe HACE.

*(A-C) Axial venoBOLD MR images reveal multiple micro-hemorrhages (small arrows) within subcortical white matter, corpus callosum, internal capsules, and cerebellar peduncles. (D-H) T_2-weighted and FLAIR sequences demonstrate confluent hyperintensities (solid arrows) representing extensive vasogenic edema involving bilateral cerebral hemispheres, corpus callosum, and periventricular white matter-imaging hallmarks of fulminant HACE.[40]

IMMUNOMODULATION AND CELLULAR EFFECTS

Leukocyte redistribution

Dexamethasone induces transient leukocytosis from neutrophil demargination while lowering lymphocyte, monocyte, and eosinophil counts. This reflects altered cell trafficking rather than marrow suppression, and reduced lymphocyte migration into brain and lung tissue helps attenuate localized inflammation.[41]

Modulation of T-cell function

Glucocorticoids inhibit Th1 and Th17 differentiation while expanding regulatory T cells (Tregs), shifting immunity toward an anti-inflammatory profile. This modulation reduces cytokine-driven endothelial injury in AMS and may also guard against hypoxia-induced autoimmune activation.[42]

Impact on gene networks

RNA-sequencing of altitude-exposed volunteers reveals that dexamethasone alters over 1,000 genes linked to immune signaling, ribosomal biogenesis, and metabolism. It suppresses cytokine-receptor, NF-κB, and HIF-1 pathways while enhancing oxidative phosphorylation and translational efficiency, indicating improved cellular adaptation to hypoxia.[43]

Pharmacokinetics and dosage considerations

Because of its long half-life and strong receptor affinity, dexamethasone permits flexible dosing schedules. Typical prophylactic regimens for AMS employ 4 mg orally every 12 hours, starting 24 hours before ascent and continuing for 48-72 hours at altitude. For treatment, 4 mg every 6 hours (oral, intramuscular, or intravenous) is recommended until symptom resolution and descent.[16,18] The inhaled budesonide offers pulmonary protection with minimal systemic exposure, although evidence for complete AMS prevention remains limited.

Dexamethasone absorption is unaffected by food and undergoes minimal first-pass metabolism. Dose modification is needed only with hepatic dysfunction or CYP3A4 inducers such as rifampicin or phenytoin.

Its prolonged half-life provides sustained protection during multi-day ascents with infrequent dosing.

Comparison with other corticosteroids

Hydrocortisone and prednisolone, though anti-inflammatory, have shorter half-lives and greater mineralocorticoid activity, limiting altitude use. Betamethasone shows comparable potency but limited evidence. Dexamethasone's longer action, efficient CNS penetration, and proven safety define its therapeutic advantage in AMS.

MOLECULAR APPROACHES

Advances in genomics, proteomics, and metabolomics have clarified physiological responses to hypoxia. While classical trials established dexamethasone's efficacy, recent high-throughput studies show it not only suppresses inflammation but also reprograms gene networks that enhance tolerance to hypobaric hypoxia (Figure 5).[44]

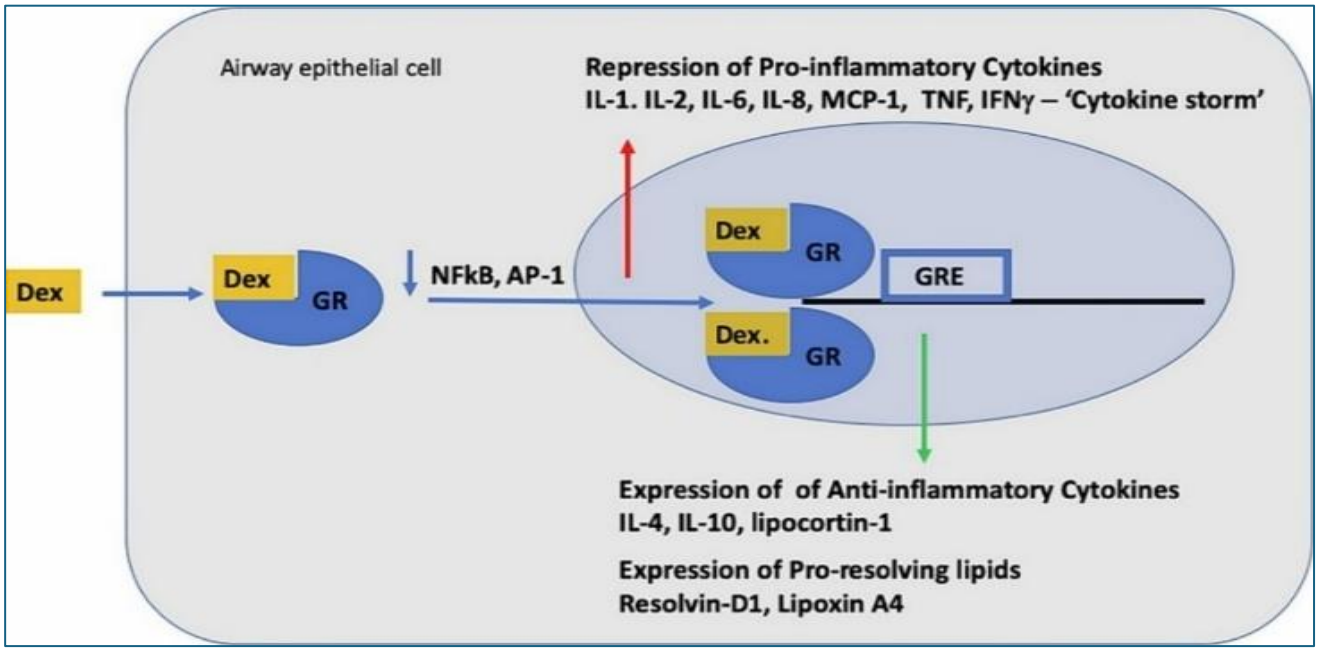

Figure 5: Anti-inflammatory and pro-resolution mechanisms of dexamethasone in hypoxia-induced inflammatory pathways.[48]

Transcriptomic insights from peripheral blood mononuclear cells

Kumar et al performed one of the most comprehensive molecular analyses of dexamethasone prophylaxis in AMS. Volunteers were exposed to simulated altitude (≈3,500 m) after receiving either dexamethasone 8 mg daily or placebo. Peripheral blood mononuclear cells (PBMCs) were collected before ascent, at altitude, and post-exposure for RNA-sequencing and flow-cytometric profiling.[28] Dexamethasone alters expression of over 1,000 genes versus placebo, notably down-regulating inflammatory mediators (IL2RA, IL6, CCL2, CXCL8, TNF) and ribosomal biogenesis pathways while up-regulating mitochondrial oxidative-phosphorylation genes. This coordinated response enhances energy efficiency and lowers inflammatory oxygen demand during hypoxia.[45]

Pathway enrichment

Functional enrichment analyses show dexamethasone markedly suppresses NF-κB and cytokine-receptor signalling, partially inhibits HIF-1α activity, and down-regulates T-cell receptor and JAK-STAT pathways. Ribosomal and translational networks are also reduced, indicating an energy-conserving immune state that limits hypoxic injury.[46]

Cellular and immunologic effects

Flow-cytometric analysis showed reduced activated T cells and increased Tregs following dexamethasone, along with decreased CD80/CD86 expression on monocytes and dendritic cells collectively dampening inflammation and endothelial stress. Serum cytokine profiling revealed lower IL-6, TNF-α, and IL-8 but higher IL-10, linking IL-6 suppression to clinical improvement. At the metabolic level, dexamethasone counteracts hypoxia-induced glycolytic shift by inhibiting HIF-1α and enhancing mitochondrial function, thereby reducing lactate buildup and preserving NAD^+ balance for cellular stability.[47]

Proteomic and metabolomic correlates

Beyond transcriptomics, proteomic analyses demonstrate consistent trends: decreased circulating acute-phase reactants (C-reactive protein, serum amyloid A) and increased antioxidant proteins (peroxiredoxins, thioredoxin). Metabolomic profiling shows higher glutathione and citrate cycle intermediates after dexamethasone prophylaxis. These shifts suggest enhanced redox buffering and mitochondrial efficiency. At the microvascular level, proteomic suppression of matrix metalloproteinases (MMP-2, MMP-9) prevents degradation of extracellular-matrix scaffolding in the blood–brain barrier, directly linking molecular data to reduced cerebral edema risk.[49] Cytokine-omics profiling under acute hypoxia (5,000 m simulation) demonstrated broad suppression of IL-17A, MCP-1, and CXCL10, alongside up-regulation of anti-inflammatory IL-1Ra. Multi-omics integration linked these responses to glucocorticoid-inducible leucine zipper (GILZ) expression, a transcriptional regulator that inhibits NF-κB and AP-1 simultaneously. Neurobehavioral assays in mice revealed significant reduction in hypoxia-induced anxiety and memory deficits following dexamethasone exposure, consistent with restored hippocampal BDNF signalling. Electron microscopy corroborated reduced astrocytic swelling and preserved synaptic architecture.[50] Thus, these experimental datasets reinforce dexamethasone's multisystem protection from mitochondrial preservation to glial stabilization bridging cellular observations with clinical benefit.

Interaction with hypoxia-inducible pathways

HIF-1 regulates hypoxic transcription, but excessive activation elevates VEGF, endothelin-1, and inflammatory mediators causing edema. Dexamethasone induces prolyl hydroxylases, promoting HIF-1α degradation and maintaining balanced signalling-preserving erythropoietic and metabolic adaptation while preventing vascular leak. It also up-regulates EPOR and Nrf2, enhancing oxygen use and antioxidant defense, thereby providing pharmacologic protection even during brief altitude exposure.[51]

Blood-brain barrier and endothelial function models

In-vitro BBB models

Human brain-microvascular-endothelial-cell (HBMEC) cultures exposed to hypoxia show tight-junction disassembly and increased permeability. Pretreatment with dexamethasone restores claudin-5 and occludin expression, decreases actin cytoskeletal stress, and normalizes trans-endothelial electrical resistance.[18] These findings experimentally confirm clinical observations of reduced headache and improved coordination after prophylaxis.

Endothelial nitric oxide balance

Dexamethasone maintains endothelial nitric-oxide synthase (eNOS) expression while suppressing inducible NOS, achieving optimal vasodilatory tone without generating excess reactive nitrogen species. This contributes to improved microcirculation and reduced oxidative stress in both pulmonary and cerebral vasculature.[52]

Animal model corroboration

In rodent altitude models (~6,000 m), hypoxia induces pulmonary hypertension, cerebral edema, and cytokine elevation. Dexamethasone pretreatment reduces pulmonary pressure, brain water, and Evans-blue leakage, indicating improved vascular integrity. Histology shows preserved alveoli and minimal perivascular edema,

paralleling human findings and confirming proposed mechanisms.[53]

Integrating molecular and clinical findings

Multi-omics analyses show that dexamethasone's efficacy in AMS stems from integrated immunometabolic and vascular stabilization suppressing cytokine activity, optimizing mitochondrial efficiency, maintaining endothelial integrity, and reducing astrocytic swelling. Collectively, these effects disrupt the core cascade of hypoxia, inflammation, and edema that drives AMS.

Emerging experimental directions

Single-cell sequencing

Single-cell RNA-seq approaches now allow cell-type-specific mapping of glucocorticoid responses. Preliminary datasets show heterogeneity among monocyte and T-cell subsets, implying that some immune populations are more steroid-responsive than others. This insight may guide precision prophylaxis where lower doses achieve optimal modulation with minimal systemic exposure.

Epigenetic mechanisms

Dexamethasone influences DNA-methylation and histone-acetylation patterns in hypoxia-responsive genes. Such epigenetic reprogramming might explain prolonged protection after drug withdrawal; a phenomenon observed in climbers descending from high camps who remain asymptomatic for several days.[13]

Integration with non-steroidal agents

Experimental co-administration with acetazolamide shows additive benefits acetazolamide accelerates ventilatory acclimatization while dexamethasone suppresses inflammatory injury. Future laboratory work is focusing on optimal dosing ratios and sequencing to maximize synergy.[54]

CONCEPTUAL MODEL OF PROTECTION

A unified framework describes dexamethasone's temporal actions in AMS: hypoxia initiates endothelial and immune activation; GR engagement triggers rapid non-genomic stabilization and reduced vascular leak within minutes, followed by genomic suppression of inflammation and mitochondrial restoration over hours to days. Prolonged antioxidant and anti-edematous effects support acclimatization or recovery, explaining its efficacy in both prophylaxis and rescue therapy. Over four decades, dexamethasone's role in altitude illness progressed from observation to evidence-based use. Early reports of symptom relief led to Ellsworth et al the first controlled trial confirming efficacy in climbers, followed by multicenter studies that established it as a prophylactic and therapeutic mainstay for AMS and HACE.

EARLY RANDOMIZED TRIALS

The Mount Rainier trial

In a double-blind, placebo-controlled study of 47 climbers on Mount Rainier (4,392 m), participants received dexamethasone 4 mg, acetazolamide 250 mg, or placebo every 8 hours starting 24 hours pre-ascent. Dexamethasone reduced headache, dizziness, and nausea by nearly 50% versus placebo and improved coordination. While acetazolamide showed similar efficacy at higher altitudes, its side effects limited use. This trial provided the first definitive evidence that dexamethasone can prevent, not only treat AMS.[16]

Other early comparative studies

Smaller trials corroborated these results across settings: Hackett et al showed dexamethasone 8 mg/day lowered AMS incidence in Himalayan trekkers; Johnson et al found reduced sleep disturbance and cognitive deficits under simulated hypoxia; and Forwand et al reported rapid recovery in AMS and early HACE. Together, these studies established dexamethasone as the only corticosteroid with proven double-blind efficacy in AMS.

Modern controlled studies

Inhaled vs oral corticosteroid trial

In a randomized, placebo-controlled trial of 138 male soldiers ascending from 400 m to 3,900 m in two days, Zheng et al. compared oral dexamethasone (4 mg BID), inhaled budesonide (200 µg BID), and placebo. AMS incidence was 30.8%, 34.8%, and 60.5%, respectively ($p<0.01$). Both corticosteroids improved FVC, FEV_1, and oxygen saturation; budesonide caused fewer systemic effects. The authors concluded that both are effective, though oral dexamethasone offers broader protection during rapid ascents.[18]

Molecularly anchored clinical validation

Building on genomic data, Kumar et al confirmed that dexamethasone prophylaxis in lowlanders ascending to 3,500 m modified inflammatory gene expression, correlating with lower AMS scores and improved oxygenation. This study provided mechanistic validation for earlier clinical findings linking symptom reduction directly to modulation of PBMC transcriptomes.[55]

Dose optimization and timing

Field studies suggest that 4 mg every 12 hours is sufficient for prophylaxis when initiated 24 hours before ascent and continued for 48-72 hours at altitude. For treatment, 4 mg every 6 hours (oral, IM, or IV) remains standard until descent and recovery. Longer courses are unnecessary and risk adrenal suppression.

Comparative efficacy with acetazolamide (Table 2)

Head-to-head comparisons have consistently shown that dexamethasone is at least as effective as acetazolamide for preventing AMS but with distinct pharmacological profiles.

Table 2: Comparative efficacy with acetazolamide.

Parameters	Acetazolamide	Dexamethasone
Mechanism	Induces metabolic acidosis, enhances ventilation	Anti-inflammatory, anti-edematous
Onset	Slow (12-24 h)	Rapid (2-6 h)
Effect on acclimatization	Promotes ventilatory adaptation	Does not promote acclimatization (symptomatic relief)
Side effects	Paresthesias, diuresis, taste alteration	Mild euphoria, insomnia, hyperglycemia
Utility	Planned ascents, gradual climbs	Rapid ascents, rescue operations

Thus, acetazolamide remains preferred for gradual trekkers, whereas dexamethasone is ideal when immediate protection or treatment is required.

Dexamethasone in HACE

HACE represents a continuum from severe AMS, characterized by ataxia and altered consciousness. Dexamethasone is life-saving in this condition. Hackett et al demonstrated dramatic improvement within hours after parenteral dexamethasone (8 mg IV followed by 4 mg q6 h).[56]

Symptom regression precedes radiologic improvement, confirming its anti-edematous efficacy. Case reports indicate near-complete neurological recovery when therapy is combined with oxygen and descent. These findings underscore dexamethasone's dual role: preventive at moderate altitudes and therapeutic in life-threatening HACE.

Dexamethasone in HAPE

Though less studied than in AMS, dexamethasone benefits HAPE via anti-inflammatory and epithelial effects. Adjunct use with descent and oxygen improves oxygenation and clears infiltrates faster.

By enhancing alveolar sodium transport and reducing capillary leak, it restores pulmonary compliance; inhaled budesonide may offer preventive value in high-risk individuals.[18]

FIELD OBSERVATIONS AND EXPEDITION DATA

Expedition data from the Himalayas, Andes, and Alps show that prophylactic dexamethasone 4 mg twice daily lowers AMS rates above 4,000 m and is used by rescue teams and pilots for rapid deployment. Rebound symptoms may follow abrupt withdrawal due to suppressed ventilatory drive, highlighting the need for gradual ascent or acetazolamide transition after steroid cessation.

Meta-analyses and systematic reviews

Recent systematic analyses integrating multiple RCTs confirm dexamethasone's efficacy: Kayser et al reviewed 12 randomized trials and reported a 65-70% risk reduction for AMS versus placebo.[15] Pooled data showed a consistent benefit across different altitudes and dosing regimens, with no severe adverse events in short-term use. Network meta-analysis ranked dexamethasone as second only to acetazolamide in prophylactic effectiveness, but first in rapid-onset symptom control.

These conclusions endorse its inclusion in international high-altitude medicine guidelines, such as those by the Wilderness Medical Society and Indian Armed Forces.

Beyond controlled trials, several large-scale observational and expedition studies across Asia, South America, and Europe have substantiated dexamethasone's clinical effectiveness.

Liu et al conducted a Chinese Army prospective cohort of 1,026 soldiers ascending from 500 m to 4,200 m within 48 hours. The incidence of AMS fell from 57 to 21% with prophylactic dexamethasone 8 mg/day, without serious adverse effects.[57] Similarly, Villafuerte et al reported that Peruvian miners receiving intermittent dexamethasone exhibited reduced work-loss days and fewer HAPE admissions.

In civilian mountaineering data, Bailey et al analyzed 15 expeditions (n=923) and found that dexamethasone prophylaxis maintained psychomotor performance and executive function compared with placebo, as measured by the Trail-Making Test B.[58]

Regional military protocols echo these outcomes: the Indian armed forces medical services trial confirmed that oral dexamethasone (4 mg bid) outperformed acetazolamide in rapid-deployment units stationed at Leh (3,500 m).[59]

In meta-surveys, Grocott et al emphasized the importance of integrating physiological data-SpO_2 trends and barometric pressure logs-into AMS evaluation to avoid diagnostic inflation. These studies, though heterogeneous, converge on one principle: dexamethasone remains the only agent with consistent cross-ethnic reproducibility in AMS prophylaxis.

Safety profile and adverse effects in clinical trials

Across studies, dexamethasone was well tolerated for short durations (≤ 5 days). Mild insomnia, mood elevation, and transient hyperglycemia were the most common complaints. Serious complications (psychosis, infection, adrenal suppression) were exceedingly rare.[18]

In the Ellsworth trial, a small subset reported mild euphoria but no psychotic reactions or withdrawal symptoms upon discontinuation. Importantly, no cases of rebound cerebral edema were recorded when proper dosing taper was observed.

Nevertheless, clinicians must remain cautious in patients with diabetes, peptic ulcer disease, or psychiatric disorders.

CLINICAL APPLICATIONS, DOSING STRATEGIES, AND SAFETY CONSIDERATIONS OF DEXAMETHASONE IN ACUTE MOUNTAIN SICKNES

Modern guidelines from the Wilderness Medical Society and the Indian Armed Forces endorse dexamethasone as a frontline agent in altitude medicine. This section outlines its real-world clinical applications covering prophylactic, therapeutic, and adjunctive uses along with dosage regimens, safety, contraindications, and practical considerations for field deployment.[59]

Prophylactic use

Dexamethasone prophylaxis is recommended for individuals ascending rapidly above 3,500 m such as military or rescue personnel, aviators, tightly scheduled trekkers, or those with prior severe AMS or HACE when acclimatization time is limited. By suppressing early inflammatory and vascular responses to hypoxia, it substitutes for physiologic acclimatization. The standard regimen is 4 mg orally every 12 hours, beginning 24 hours before ascent and continuing for 48-72 hours (maximum 5 days); a 2 mg every 6 hours schedule suits low-weight or insomnia-prone users. Its long half-life (36-54 h) maintains protection despite missed doses. Lightweight, stable tablets make it ideal for field use, and defense or rescue teams often include pre-packed "AMS kits" for supervised self-administration.

Therapeutic use in AMS and HACE

Therapeutic dexamethasone is indicated for moderate to severe AMS (Lake Louise score ≥5 with headache and nausea), cases unresponsive to rest or acetazolamide, early or established HACE with ataxia or confusion, and when descent or oxygen therapy is delayed.[18] The recommended regimen is an initial 8 mg dose given orally, intramuscularly, or intravenously, followed by 4 mg every 6 hours until symptoms resolve; then taper to 4 mg every 12 hours for 24 hours to prevent rebound edema. IM, IV, and oral routes are equally effective once nausea subsides.

RESPONSE PROFILE

Most patients experience symptomatic relief within 6-8 hours, with restoration of coordination and mental clarity in 24 hours. In HACE, neurological recovery may take 48-72 hours if combined with oxygen and descent.

Role in HAPE

Although AMS and HAPE differ in primary mechanisms, both involve endothelial inflammation and capillary leak. Dexamethasone enhances alveolar fluid clearance via Na^+/K^+-ATPase and epithelial sodium channel up-regulation, reducing edema and improving oxygenation. As an adjunct to oxygen and nifedipine, it hastens recovery and shortens hospitalization. Prophylaxis is reserved for recurrent HAPE. In children over 8 years, 0.1 mg/kg every 6 hours is effective, while acetazolamide is preferred in younger cases unless severe AMS or HACE occurs. Elderly patients need glucose and mood monitoring, but short supervised courses are generally safe.

Routes of administration

Dexamethasone can be administered via multiple routes depending on clinical context. The oral route is preferred for routine prophylaxis and mild AMS due to high bioavailability. Intramuscular injection is suitable in field settings or when vomiting prevents oral intake, while intravenous delivery ensures rapid action in severe or unconscious HACE cases. Inhaled corticosteroids such as budesonide offer pulmonary protection and reduced systemic effects in individuals at risk of HAPE.[18]

Combination therapy and treatment algorithms (Dexamethasone + acetazolamide)

Dexamethasone and acetazolamide act synergistically acetazolamide boosts ventilation while dexamethasone prevents inflammatory edema. Field regimens advise acetazolamide 250 mg BID with dexamethasone 4 mg BID for those with prior severe AMS. For moderate AMS, halt ascent, rest, give dexamethasone 4 mg PO/IM every 6 hours, add acetazolamide if not started, and provide oxygen if SpO_2<85%. In HACE, descend ≥500 m immediately, administer dexamethasone 8 mg IV/IM followed by 4 mg every 6 hours, and use oxygen or a hyperbaric bag for ≥24 h after recovery. Common short-term effects include transient insomnia, euphoria, gastric discomfort, and mild hyperglycemia; psychiatric symptoms are rare and resolve after withdrawal. No infection risk is seen with ≤5-day courses. Repeated or prolonged use can cause adrenal suppression, mood change, and glucose intolerance; hence courses >5 days need medical oversight. Abrupt cessation during ascent may cause rebound AMS-tapering or switching to acetazolamide avoids this. Field clinicians should

document dose, timing, Lake Louise score, and response, and monitor glucose and mood if therapy exceeds 3 days. A dexamethasone usage register is recommended for audit and training.

Table 3: Practical guide: dexamethasone dosing and supportive measures.

Clinical scenario	Dexamethasone regimen	Duration	Adjunct measures
Rapid ascent without acclimatization	4 mg PO q12 h starting 24 h pre-ascent	2-3 days	Hydration + rest
Moderate AMS	4 mg PO/IM q6 h	2-3 days	Rest ± acetazolamide
Severe AMS / HACE	8 mg IV/IM → 4 mg q6 h	Until descent	Oxygen + hyperbaric bag
Recurrent HAPE risk	4 mg PO q12 h	3 days	Add nifedipine if needed

Over six decades of investigation have transformed dexamethasone from an empirical anti-inflammatory agent into a scientifically validated cornerstone of high-altitude medicine. From the pioneering Mount Rainier trial to recent transcriptomic analyses, the drug's efficacy and mechanistic depth are firmly established. Yet, as global exposure to altitude increases through adventure tourism, aviation, and military deployment, questions regarding precision use, safety in diverse populations, and long-term implications remain (Table 3).

PRECISION PROPHYLAXIS

Polymorphisms in NR3C1, HIF-1α, IL-6, and VEGF genes influence hypoxia sensitivity and steroid responsiveness. Identifying such variants may help predict who benefits most from dexamethasone versus acetazolamide; for example, carriers of the IL-6-174 G/C genotype often show better steroid response. Genotype-guided dosing could reduce overuse and individualize prophylaxis in expedition settings. Epigenetic regulation via DNA methylation and histone acetylation of GR-related genes and sex-dependent hormonal modulation also affect steroid sensitivity, suggesting sex-specific adjustments may enhance safety. Advances in multi-omics monitoring now enable portable detection of IL-6 or VEGFA expression as early AMS predictors. Coupled with wearable oximetry and heart-rate tracking, these data can create personalized dashboards guiding dexamethasone initiation or tapering-transforming prophylaxis from symptom-based to biologically driven.

Novel drug-delivery platforms

Inhaled budesonide provides pulmonary protection comparable to oral dexamethasone with fewer systemic effects.[18] Emerging nano-encapsulated or liposomal inhalers may enhance lung targeting and minimize adrenal suppression, while intranasal formulations could deliver rapid CNS relief in early AMS.

Long-acting injectables and microsphere depots sustaining plasma levels for 3-5 days are under study for extended climbs, and transdermal patches releasing continuous micro-doses may benefit military operations. These advances could shift steroid prophylaxis from repeated dosing to single-application delivery systems.

Combination and multimodal strategies

Combining acetazolamide with dexamethasone synergistically enhances ventilation and controls edema, offering broader AMS protection confirmed by multiple trials. Adjunctive antioxidants (vitamin C, E, N-acetylcysteine) and NO donors (L-arginine, L-citrulline) further support endothelial stability and oxygen use. While gradual ascent and hydration remain primary preventive measures, dexamethasone serves as supportive therapy rather than a substitute.

Guideline differences persist CDC (2020) restricts use to rescue, the European Alpine Consensus (2021) allows prophylaxis above 3,800 m, and ICMR (2022) includes both preventive and therapeutic use.

Safety, regulation, and ethical considerations

Unsupervised dexamethasone use among recreational climbers can mask early AMS and cause rebound illness on withdrawal, emphasizing the need for physician oversight and education by mountaineering and military organizations. Repeated short courses may suppress the HPA axis and cause transient hyperglycemia; glucose and cortisol recovery should be monitored in long-term altitude personnel. Although dexamethasone may enhance mood and endurance, prompting anti-doping restrictions, medically supervised use for AMS prophylaxis remains ethical and distinct from performance enhancement.

Research gaps and priorities

Despite extensive data, significant gaps persist. Future priorities include defining the minimal effective duration for prophylaxis, assessing long-term endocrine and metabolic safety, and studying under-represented groups such as women and children. Pharmacogenomic validation and exploration of steroid–microbiome interactions may improve personalization.

Environmental factors like cold, dehydration, and caloric deficit also merit study for their effects on steroid kinetics. Addressing these gaps will refine dexamethasone's role in precision altitude pharmacology-marking the evolution of altitude medicine from symptomatic relief to molecular modulation.[60]

NEXT-GENERATION THERAPEUTICS

Selective glucocorticoid receptor modulators (SGRMs) are emerging to preserve anti-inflammatory efficacy while reducing systemic effects. Integration with AI-driven analytics from wearable sensors may soon allow dynamic, personalized dexamethasone dosing. Machine-learning models using heart-rate variability, oxygen saturation, and barometric data can predict AMS onset up to 18 hours in advance, enabling automated micro-dosing via programmable patches. Computational modelling has identified SGRMs such as AL-2123 and Mapracorat, which demonstrate potent anti-inflammatory action with minimal cortisol suppression in hypobaric models. Additionally, CRISPR-mediated up-regulation of HIF-prolyl-hydroxylase-2 enhances hypoxia tolerance, potentially complementing pharmacologic prophylaxis. Together, these innovations point toward a future of precision, data-driven altitude medicine integrating genomics, AI, and advanced steroid design.

CONCLUSION

Dexamethasone stands as the benchmark pharmacologic safeguard against AMS. Its dual ability to prevent AMS and reverse HACE makes it irreplaceable in high-altitude operations. The drug's effects spanning genomic, cellular, and vascular stabilization counteract the central triad of AMS pathophysiology: hypoxia, inflammation, and edema. As research advances from molecular to precision paradigms, dexamethasone will continue evolving from a general anti-edematous drug into a targeted genomic modulator of hypoxia adaptation. When used rationally guided by molecular insights and ethical restraint, it will remain the gold standard for high-altitude pharmacotherapy, safeguarding climbers, soldiers, and travelers in the world's most extreme environments.

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