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MULTISYSTEM ADVERSE EFFECTS OF ISOTRETINOIN: MECHANISTIC INSIGHTS AND CLINICAL IMPLICATIONS

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ABSTRACT

Isotretinoin (13-cis-retinoic acid) remains the most effective systemic therapy for severe acne, exerting its therapeutic action through modulation of retinoic acid (RAR) and retinoid X (RXR) receptors that regulate cell differentiation, apoptosis, and lipid metabolism. However, these same receptor-mediated pathways underlie a range of multisystem adverse effects. This review provides an updated synthesis of isotretinoin's systemic toxicity profile, focusing on mechanistic insights and clinical relevance. Mucocutaneous reactions such as cheilitis and xerosis are the most frequent and predictable effects, reflecting sebaceous suppression. Hepatic enzyme elevations and dyslipidemia occur in a dose-dependent yet reversible manner, necessitating routine laboratory surveillance. Musculoskeletal, ocular, and neuropsychiatric effects are infrequent, generally mild, and self-limiting, though psychiatric monitoring remains advisable in predisposed individuals. Gastrointestinal and endocrine disturbances, including subclinical hypothyroidism, have been reported but lack strong causal evidence. Hematologic and renal alterations are minor and transient. The most critical safety concern remains isotretinoin's potent teratogenicity, emphasizing the need for strict contraceptive protocols and post-therapy washout periods. Overall, isotretinoin's adverse effects largely reflect its pharmacodynamic actions and are manageable through individualized dosing and systematic monitoring. Understanding the mechanisms and risk factors underlying these reactions is essential for optimizing therapeutic safety and patient outcomes.

KEYWORDS

Isotretinoin, Adverse Effects, Safety Profile, Retinoid Receptors

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1. Introduction

Isotretinoin (13-cis-retinoic acid) (ISO) is a first-generation retinoid widely recognized as one of the most effective systemic treatments in dermatology, primarily indicated for severe or treatment-resistant acne vulgaris [1]. Introduced into clinical use in the early 1980s, ISO acts as a stereoisomer of all-trans retinoic acid, exerting its effects through the activation of retinoic acid (RAR) and retinoid X (RXR) receptors [2–4]. These nuclear receptors regulate gene transcription pathways involved in cell differentiation, apoptosis, and tissue remodeling, which together account for the drug's broad biological and therapeutic impact. Clinically, ISO reduces sebaceous gland activity, suppresses Cutibacterium acnes, and normalizes keratinization, resulting in long-term remission in most patients [3,5–7]. Beyond its use in acne, ISO demonstrates efficacy in various inflammatory and keratinization disorders, including rosacea, lichen planus, and actinic keratosis [3,8,9]. However, the same receptor-mediated mechanisms that underpin its therapeutic action can also provoke systemic adverse effects involving multiple organ systems [10–13]. Among the biochemical alterations observed during therapy, changes in lipid metabolism are common but usually reversible after treatment cessation [14–18].

Due to its extensive systemic activity and strong influence on cellular regulatory networks, ISO therapy requires careful clinical supervision and ongoing safety evaluation [19,20]. Furthermore, its potent teratogenicity, driven by dysregulation of retinoid signaling during embryogenesis, remains a major concern in clinical practice [21–23]. Given the complex pharmacodynamics of ISO and the potential for multisystem involvement, a detailed understanding of its adverse effects is crucial. This review aims to summarize the current knowledge on the systemic toxicities of ISO, explore their mechanistic foundations, and highlight their implications for evidence-based clinical management.

2. Methodology

We conducted a narrative review based on a comprehensive search of the scientific literature. Databases including PubMed, Scopus, Web of Science, and Google Scholar were queried for publications related to ISO, its pharmacology, and systemic adverse effects. Search terms included combinations of: "isotretinoin," "adverse effects," "RAR/RXR receptors," "retinoid toxicity," "dyslipidemia," "teratogenicity," "musculoskeletal effects," "neuropsychiatric effects," and "safety profile." Priority was given to peer-reviewed clinical studies, mechanistic research, systematic reviews, and meta-analyses published within the past 5 years, although earlier foundational studies were included when mechanistically relevant.

3. Mechanistic and Pharmacodynamic Basis of Isotretinoin Action

3.1. Pharmacokinetic Profile and Metabolic Activation

ISO is a lipophilic retinoid that undergoes extensive hepatic metabolism following oral administration. It is rapidly absorbed within 2–4 hours and metabolized via the cytochrome P450 microsomal enzyme system, primarily involving CYP2C8, CYP2C9, CYP3A4, and CYP2B6 isoenzymes. These oxidative reactions generate three main metabolites, 4-oxo-isotretinoin, all-trans retinoic acid (ATRA), and 4-oxo-retinoic acid (4-oxo-tretinoin), which exist in a state of reversible interconversion [24,25].

The plasma concentration of 4-oxo-isotretinoin typically exceeds that of ISO by two- to fourfold within six hours post-administration, with steady-state levels achieved after approximately one week. The drug exhibits a half-life of 7–37 hours, while its metabolites persist for up to 50 hours. It is >99% bound to plasma albumin, displays limited tissue storage, and shows no progressive accumulation in hepatic or adipose compartments during long-term therapy [25].

Crucially, ISO acts as a prodrug, undergoing intracellular isomerization to its active metabolite ATRA. This conversion, particularly pronounced in sebocytes, allows selective activation of nuclear retinoid signaling while minimizing hepatic enzyme induction [26].

3.2. Nuclear Receptor Signaling and Gene Regulation

ATRA exerts its biological activity through high-affinity binding to RARs and RXRs. The heterodimeric complexes formed by these receptors interact with retinoic acid response elements (RAREs) in target gene promoters, initiating transcriptional programs that govern cell differentiation, apoptosis, and lipid metabolism [26]. Through these nuclear pathways, ISO modulates the expression of a wide range of structural and signaling proteins, downregulating cytokeratins 1, 10, and 14, filaggrin, and matrix metalloproteinases (MMPs), while upregulating cytokeratins 7, 13, and 19, laminin B1, and interleukin-1 (IL-1) [24,27]. This reprogramming of gene expression normalizes keratinocyte differentiation, suppresses infundibular hyperkeratinization, and prevents comedone formation, thus targeting the early pathogenic stages of acne [27].

In addition to receptor-mediated signaling, ISO activates p53-dependent transcriptional cascades that enhance the expression of genes involved in cell cycle arrest (CDKN1A/p21), autophagy (ATG7), and programmed cell death (FOXO1, FOXO3, CASP1). Simultaneously, it suppresses the transcription of genes regulating androgen signaling (AR), growth factor activity (IGF1, IGF1R), cell survival (BIRC5), and lipid biosynthesis (SREBF1), thereby attenuating sebocyte proliferation and sebum synthesis [26,28].

Furthermore, ISO's pro-apoptotic activity involves stimulation of the TNF-related apoptosis-inducing ligand (TRAIL) pathway. Activation of death receptors DR4 and DR5 triggers caspase-8 and caspase-3 cascades, leading to apoptotic elimination of sebocytes and keratinocytes, a central event in the reduction of sebaceous gland volume [28].

3.3. Cellular and Clinical Effects: Sebosuppression, Lipid Modulation, and Immunoregulation

At the tissue level, ISO induces a profound reduction in sebaceous gland size and activity, often up to 90%, through direct inhibition of sebocyte proliferation and lipogenesis. The composition of surface lipids is altered-wax esters and squalene decline, whereas cholesterol and ceramide fractions increase, reflecting normalized lipid metabolism [29]. Additionally, ISO competitively inhibits 3-hydroxysteroid oxidation by retinol dehydrogenase, reducing dihydrotestosterone and androstanedione formation and further contributing to its sebosuppressive efficacy [30]. Beyond sebaceous regulation, ISO exhibits broad anti-inflammatory and immunomodulatory effects. It inhibits monocyte and neutrophil chemotaxis, reduces TNF-α and nitric oxide production, and may enhance cathelicidin peptide expression, supporting antimicrobial defense and tissue repair [31]. These combined mechanisms alter the follicular microenvironment, suppressing Cutibacterium acnes colonization and dampening inflammatory cytokine activity [27,31].

Collectively, ISO's multifaceted mechanism, integrating metabolic activation, nuclear receptor modulation, apoptosis induction, lipid reprogramming, and immune regulation, accounts for both its exceptional clinical efficacy in severe acne and its broad systemic biological effects [26-31].

4. Adverse Effects of Isotretinoin

ISO therapy is linked to a broad spectrum of systemic and cutaneous adverse reactions that generally depend on dose intensity and treatment duration, reflecting the drug's impact on cellular differentiation, lipid metabolism, and neuroendocrine signaling (Table 1) [32,33]. The most prevalent effects are mucocutaneous, including cheilitis, xerosis, and impairment of the epidermal barrier, which result from the suppression of sebaceous gland function and reduced hydration of the skin [33]. These symptoms occur in the vast majority of patients but are usually mild, reversible, and effectively controlled with topical moisturizers [32]. Systemic manifestations may involve hepatic and lipid alterations, musculoskeletal discomfort, and neuropsychiatric disturbances. Temporary increases in hepatic transaminases or serum lipid concentrations are observed in roughly one-fifth to one-third of patients and typically normalize after dose reduction or treatment cessation [33]. Musculoskeletal complaints such as stiffness, myalgia, or pain are attributed to retinoid-mediated effects on collagen turnover and bone metabolism, whereas fatigue and mood changes are likely associated with retinoid receptor modulation within central neurotransmission pathways [32].

Overall, ISO's toxicity profile is considered predictable and dose-dependent. Lower or intermittent dosing regimens (≤0.5 mg/kg/day) are effective in maintaining therapeutic outcomes while decreasing the likelihood of systemic complications. Combination strategies, such as the use of low-dose ISO alongside light-based treatments, have also been shown to improve tolerability by minimizing cumulative exposure [33]. In conclusion, the adverse effects of ISO reflect its pharmacologic mechanisms, are typically reversible, and are best mitigated through individualized dosing and regular clinical and laboratory monitoring [32,33].

Table 1. Summary of Multisystem Adverse Effects of Isotretinoin: Prevalence, Mechanistic Basis, Clinical Characteristics, and Monitoring Recommendations

System	Mechanistic Basis	Typical Clinical Presentation	Frequency / Severity	Monitoring & Management
Mucocutaneous	Sebaceous gland suppression; altered keratinocyte differentiation; reduced epidermal lipid content.	Cheilitis, xerosis, epistaxis, dermatitis; less commonly: telogen effluvium, hair thinning.	Very common (>80–90%); predictable and dose-dependent; reversible.	Emollients, nasal lubricants, photoprotection; dose reduction if severe dermatitis; reassurance regarding reversibility.
Hepatic	Retinoid-related modulation of hepatic enzymes; transient metabolic adaptation.	Mild ↑ALT/AST; usually asymptomatic.	Uncommon (1–3%); reversible.	Baseline and periodic liver enzymes; dose reduction or interruption if ALT/AST >3× ULN.
Lipid metabolism	Retinoid effects on lipid synthesis and metabolism; decreased lipoprotein lipase activity.	↑TG, ↑TC/LDL; ↓HDL.	Common (TC/TG elevation in 20–30%; HDL decrease in 10–20%).	Fasting lipid panel baseline + early follow-up; lifestyle modification; dose reduction; discontinue ISO if TG > 800–1000 mg/dL due to pancreatitis risk.
Neuropsychiatric	Central retinoid signaling; individual susceptibility; confounding by acne severity.	Mood fluctuations, anxiety, transient depressive symptoms (rare).	Rare; no proven causal relationship; overall mood often improves during therapy.	Psychiatric history screening; PHQ-9/GAD-7 follow-up; close monitoring in at-risk individuals; discontinue ISO if severe symptoms emerge.

Ocular	Meibomian gland dysfunction; instability of lipid tear layer; transient choroidal vascular effects.	Dry eye, irritation, blepharitis; impaired night vision (rare).	Common for dry eye; other effects rare and reversible.	Artificial tears (preservative-free), limit contact lens wear; Schirmer test if symptomatic; discontinue if severe keratopathy.
Musculoskeletal	Retinoid modulation of bone turnover, enthesis inflammation, and muscle metabolism.	Low back pain, myalgia, arthralgia; sacroiliitis (rare); elevated CK.	Musculoskeletal symptoms ~20–30%; sacroiliitis rare; CK elevation 1–6%.	Clinical exam; CK testing if myalgia; NSAIDs; discontinue ISO for suspected sacroiliitis.
Gastrointestinal	Proposed mechanisms: mucosal irritation; metabolic alterations (hypertriglyceridemia-induced pancreatitis). No evidence for IBD causality.	Dyspepsia; abdominal discomfort; very rare pancreatitis; no increased risk of IBD.	GI symptoms <2%; pancreatitis extremely rare.	Clinical follow-up; lipid monitoring; urgent evaluation for abdominal pain with TG elevation.
Endocrine–metabolic	RAR/RXR-mediated modulation of thyroid transcription and metabolism.	Mild ↑TSH; ↓fT3/fT4; clinically silent.	Uncommon; typically subclinical and reversible.	Thyroid function tests in at-risk patients (or if symptomatic); no therapy usually required.
Neurological	Retinoid effects on CSF dynamics; interaction with tetracyclines.	Mild headaches; very rare pseudotumor cerebri.	Headache 2–4%; intracranial hypertension extremely rare.	Avoid tetracyclines; urgent evaluation for headache + visual symptoms; discontinue ISO if PTC suspected.
Hematologic	Transient modulation of bone marrow activity; IL-6–linked platelet effects.	Mild leukopenia, thrombocytopenia, or changes in MPV; typically asymptomatic.	Uncommon; values remain within normal range.	CBC monitoring in selected patients; discontinue if significant cytopenia occurs.
Renal	Minimal renal impact; rare lab alterations in oncology combination studies.	Mild, reversible changes in creatinine or urinalysis (very rare).	Very rare.	Renal monitoring only in patients with comorbidities or nephrotoxic co-therapy.
Teratogenicity	Excessive embryonic RAR/RXR activation → disruption of neural, craniofacial, cardiac, and thymic development.	Severe congenital malformations; miscarriage if exposed during pregnancy; no risk from paternal exposure.	Critical risk; 20–35% major malformations with first-trimester exposure.	Mandatory contraception; monthly pregnancy tests; strict washout period after therapy; immediate cessation and teratology consultation if exposure occurs.

Abbreviations: ISO — isotretinoin; ATRA — all-trans retinoic acid; TG — triglycerides; TC — total cholesterol; LDL — low-density lipoprotein; HDL — high-density lipoprotein; ALT — alanine aminotransferase; AST — aspartate aminotransferase; CK — creatine kinase; IBD — inflammatory bowel disease; TFT — thyroid function tests; TSH — thyroid-stimulating hormone; fT3 — free triiodothyronine; fT4 — free thyroxine; PTC — pseudotumor cerebri; MRI — magnetic resonance imaging; OCT — optical coherence tomography.

4.1. Mucocutaneous Adverse Effects of Isotretinoin

The mucocutaneous adverse effects of ISO primarily result from its pharmacologic suppression of sebaceous gland activity, which disrupts epidermal lipid homeostasis and compromises barrier integrity. By reducing sebum secretion, ISO diminishes the skin's natural lubrication and predisposes patients to transepidermal water loss, dryness, and epithelial irritation. These effects are mechanistically linked to the drug's influence on RAR receptors expressed in epidermal and glandular tissues, altering keratinocyte differentiation and sebaceous function [34].

Clinically, these mechanisms most frequently manifest as cheilitis and xerosis, which occur in the majority of treated individuals and are regarded as dose-dependent yet reversible adverse effects. Cheilitis typically presents as lip inflammation, fissuring, and scaling, while xerosis often involves generalized dryness affecting the face, trunk, and extremities, occasionally accompanied by pruritus or facial dermatitis. Despite their high prevalence, these conditions are usually mild, self-limiting, and manageable through topical emollients and adequate hydration [34]. Less common mucocutaneous manifestations include telogen effluvium and diffuse hair thinning, reflecting ISO's secondary effects on follicular cycling. A prospective study by Kaya İslamoğlu and Altınyazar demonstrated that patients receiving 0.5 mg/kg/day ISO for three months exhibited no statistically significant changes in total hair count, density, or anagen-to-telogen ratio, suggesting that short-term therapy exerts minimal measurable impact on hair physiology [35]. Complementary findings from Gencebay et al. provide further insight into ISO's cutaneous profile. In a six-month prospective analysis, patients experienced a 36% reduction in sebum production and a 79% increase in skin hydration, while skin elasticity remained unchanged [36]. These observations confirm ISO's potent sebosuppressive properties and indicate that the apparent dryness reported clinically may occur despite measurable improvements in epidermal water retention.

In summary, ISO-induced mucocutaneous reactions are dose-related, reversible, and mechanistically consistent with retinoid-mediated modulation of sebaceous and epithelial physiology. They represent predictable pharmacodynamic extensions rather than unpredictable toxicities, emphasizing the importance of individualized dosing and proactive skincare to optimize therapeutic tolerance and adherence [34-36].

4.2. Hepatic and Lipid Adverse Effects of Isotretinoin

ISO therapy can lead to mild, transient alterations in hepatic function and lipid metabolism, reflecting the compound's systemic retinoid activity. The most frequent biochemical changes include elevations in serum aminotransferases as well as dyslipidemia characterized by increased total cholesterol (TC), low-density lipoprotein (LDL), and triglyceride (TG) levels, accompanied by a reduction in high-density lipoprotein (HDL) concentrations [37]. These effects are generally subclinical, dose-dependent, and reversible upon treatment modification or cessation.

In a large retrospective cohort study involving 468 patients treated with various ISO formulations, Boutros Soutou et al. reported hepatic enzyme and lipid abnormalities as the most frequent laboratory disturbances observed during therapy. The incidence of elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was relatively low, occurring in 1.9% and 2.8% of patients, respectively, whereas the overall rate of liver function test abnormalities reached 11% among individuals receiving Acnotren® ($p = 0.009$). Dyslipidemic responses were more prevalent, with hypercholesterolemia (20.9%) and hypertriglyceridemia (10.5%) most commonly associated with Roaccutane® and Curacné® formulations. A statistically significant correlation between triglyceride elevation and higher body weight ($p = 0.004$) suggested that individual metabolic predisposition contributes to the magnitude of ISO-induced lipid changes [38,39].

Prospective clinical data further corroborate these findings, showing consistent increases in ALT, AST, total cholesterol, and triglycerides during therapy, coupled with a concomitant decrease in HDL cholesterol. Importantly, all deviations normalized following dose reduction or treatment discontinuation, and no cases of clinically apparent hepatotoxicity were documented, supporting the interpretation that these alterations reflect transient metabolic adaptation rather than irreversible hepatocellular damage [39].

Overall, ISO-induced hepatic and lipid disturbances represent predictable, pharmacologically mediated effects that are typically benign and reversible. Routine laboratory monitoring of liver enzymes and lipid profiles throughout therapy remains essential for early detection and management of abnormalities. Adjusting the dosage or implementing dietary and lifestyle modifications can effectively mitigate these effects and ensure continued therapeutic safety and efficacy [37-39].

4.3. Neuropsychiatric Adverse Effects of Isotretinoin

Neuropsychiatric adverse reactions, primarily encompassing depressive and anxiety-related symptoms, have been described in association with ISO therapy; however, their causal relationship remains uncertain [40]. In a comprehensive meta-analysis including 31 clinical studies, Huang and Cheng evaluated the potential link between ISO exposure and depressive symptomatology among patients with acne. The pooled analysis revealed no statistically significant difference in depression scores between ISO-treated individuals and controls (SMD −0.334, 95% CI −0.680 to 0.011). Moreover, the overall prevalence of depression declined following therapy (RR 0.588, 95% CI 0.382–0.904), and mean depression scores significantly decreased relative to baseline values (SMD −0.335, 95% CI −0.498 to −0.172). These findings indicate that ISO does not exacerbate depressive symptoms and may, in fact, contribute to psychological improvement secondary to acne resolution. Nonetheless, the authors emphasized that individual susceptibility to affective alterations cannot be completely excluded, warranting continuous psychiatric surveillance throughout treatment [41].

Further evidence supporting these observations was provided by Botsali et al., who conducted a six-month prospective study involving 55 adolescents, including 38 patients treated with ISO and 17 receiving systemic antibiotics. Participants undergoing ISO therapy demonstrated enhanced executive and attentional performance, as measured by neurocognitive assessments such as the Stroop, digit span, and trail-making tests. A transient increase in depressive symptoms was observed during the third month of treatment ($p = 0.011$); however, symptom scores subsequently returned to baseline levels, and no subjects fulfilled the diagnostic criteria for major depressive disorder. Notably, approximately 44% of individuals who experienced temporary mood alterations had a personal or familial history of psychiatric illness, suggesting that preexisting vulnerability factors, both genetic and environmental, may predispose certain individuals to affective side effects [42].

Taken together, available evidence consistently indicates that ISO does not significantly increase the risk of depression or major psychiatric disorders. In most cases, treatment is associated with an overall improvement in psychological well-being concurrent with dermatologic recovery. Nevertheless, given the possibility of rare idiosyncratic mood disturbances in predisposed individuals, vigilant psychiatric monitoring and individualized clinical assessment remain essential components of safe ISO management [41,42].

4.4. Ocular Adverse Effects of Isotretinoin

Ocular adverse effects constitute a notable component of ISO's systemic safety profile, with dry eye syndrome (sicca) representing the most frequently observed manifestation. This condition has been attributed to atrophic alterations of the meibomian glands and disturbances in the tear film composition and stability [43]. The resulting deficiency in the lipid layer of the tear film leads to increased evaporation, ocular surface dryness, and irritative symptoms such as burning, foreign body sensation, and photophobia. These reactions typically develop during therapy and resolve upon discontinuation, indicating a dose-dependent and reversible mechanism of toxicity [44].

In a prospective clinical study, Polat and Kükner reported a statistically significant reduction in tear secretion following 4–7 months of ISO administration ($p < 0.001$). The authors linked this decline to functional impairment of the meibomian glands and instability of the lipid component of the tear film. Despite these biochemical and structural alterations, visual acuity and contrast sensitivity remained unaffected, suggesting that ocular surface dryness represents the predominant early adverse event rather than a direct visual disturbance. The majority of symptoms subsided after cessation of treatment, confirming the transient nature of these changes [44].

Further insights were provided by Yavuz and Ozcimen, who observed a temporary increase in choroidal thickness, particularly in the temporal and superotemporal quadrants, as determined by optical coherence tomography. This observation was interpreted as a consequence of transient vascular dilation and altered choroidal perfusion, without corresponding abnormalities in the visual field or retinal nerve fiber layer. These findings support the concept that ISO's ocular toxicity is predominantly functional and self-limiting, with minimal risk of permanent posterior segment involvement [45].

Collectively, available clinical data indicate that ISO-induced ocular adverse effects are reversible, dose-related, and largely confined to the ocular surface and vascular structures. To ensure safe therapy, routine ophthalmologic evaluation, including Schirmer's test and tear breakup time assessment, is recommended, especially for patients with preexisting dry eye disease or contact lens intolerance. Early detection and supportive management enable effective control of ocular symptoms and contribute to maintaining patient comfort and treatment adherence [43-45].

4.5. Musculoskeletal Adverse Effects of Isotretinoin

Musculoskeletal complications constitute a recognized but generally reversible aspect of ISO therapy, reflecting the drug's influence on bone and muscle homeostasis through retinoid receptor–mediated pathways. Reported symptoms most frequently include low back pain, myalgia, arthralgia, tendinopathy, and sacroiliitis, typically arising within the first few months of treatment. According to a recent systematic review by Almutairi et al., sacroiliitis represented the most clinically significant musculoskeletal adverse event. The analysis demonstrated a correlation between the cumulative dose of ISO and the risk of developing low back pain, while no association was found with HLA-B27 positivity, suggesting a mechanism independent of classical spondyloarthropathic predisposition. Notably, discontinuation of ISO and administration of anti-inflammatory therapy led to complete symptom resolution in the majority of cases, confirming the reversible and self-limiting nature of these manifestations [46].

Further evidence from a prospective observational study by Alkan et al. revealed rheumatologic complaints in 23.1% of patients treated with ISO at an average daily dose of 30 mg for 4–6 months. The most common presentations were inflammatory low back pain, Achilles enthesopathy, and unilateral sacroiliitis, none of which were observed in the control group receiving tetracycline, supporting a direct link between ISO exposure and inflammatory musculoskeletal reactions. Radiologic assessment using MRI and ultrasonography demonstrated bone marrow edema and enthesitic changes, although C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) remained within normal limits. The absence of HLA-B27 positivity in affected patients further indicates a non–HLA-associated inflammatory mechanism. All cases resolved within three months after treatment cessation, reinforcing the transient character of these effects [47]. In addition, Yesilkaya et al. documented asymptomatic elevations in serum creatine kinase (CK) in 3.4% of ISO-treated patients, with only one individual reporting mild myalgia. These abnormalities normalized after drug withdrawal, suggesting a dose-dependent and reversible myopathic response to ISO exposure [48]..

Collectively, available clinical evidence supports the conclusion that ISO can transiently affect the musculoskeletal system via retinoid-induced modulation of bone turnover and muscle metabolism. Although such adverse effects are typically mild and self-limited, clinicians should maintain vigilance for musculoskeletal pain, fatigue, or laboratory abnormalities during therapy. Periodic monitoring of serum CK levels and appropriate clinical assessment are recommended to ensure early detection and safe management of these reversible reactions [47,48].

4.6. Gastrointestinal Adverse Effects of Isotretinoin

Gastrointestinal adverse reactions to ISO remain uncommon but have been discussed in the context of inflammatory bowel disease (IBD). Although case reports suggest a possible link, current evidence does not confirm a causal relationship. Proposed mechanisms include inhibition of intestinal epithelial regeneration, immune activation, and alterations in lipid metabolism that could, in theory, predispose to ulcerative colitis in susceptible individuals [49].

Rarely, ISO has been associated with acute pancreatitis, either secondary to marked hypertriglyceridemia or as an idiosyncratic event without a clear metabolic trigger. The drug is classified as a category III cause of drug-induced pancreatitis, meaning that supportive but inconsistent evidence exists [50]. Comprehensive epidemiologic data refute a significant connection between ISO and IBD. A meta-analysis by Lee et al. involving over 9 million individuals found no increased risk for Crohn's disease or ulcerative colitis (OR 1.08; 95% CI 0.82–1.42), nor any dose- or duration-dependent trends [51]. Similarly, Kapała et al. observed that mild gastrointestinal symptoms, such as nausea, abdominal discomfort, or diarrhea, occurred in less than 2% of cases and resolved spontaneously [52].

Overall, ISO's gastrointestinal effects are rare, mild, and reversible, typically representing transient mucosal irritation rather than chronic or inflammatory pathology. Periodic clinical assessment and lipid monitoring are advised, especially in patients with prior gastrointestinal disease or hypertriglyceridemia [51,52]

4.7. Endocrine–Metabolic Adverse Effects of Isotretinoin

ISO may transiently affect thyroid hormone balance through retinoid receptor–mediated modulation of thyroidal gene transcription and metabolism. This is typically characterized by an increase in thyroid-stimulating hormone (TSH) and mild reductions in free triiodothyronine (fT3) and free thyroxine (fT4) levels [53].

In a prospective study involving 50 patients treated with ISO (0.5–1 mg/kg/day) for four months, Kotb et al. observed significant increases in TSH and decreases in T3 and T4 concentrations ($p < 0.001$). All values remained within normal reference ranges, and no clinical signs of hypothyroidism were detected. Hormonal

levels normalized after discontinuation, indicating a reversible subclinical pattern [54]. A similar pattern was confirmed by Yıldırım et al. in a six-month prospective study of 51 patients receiving cumulative doses of 120 mg/kg. TSH levels increased while fT3 and fT4 decreased at both the third and sixth months ($p < 0.01$), yet all participants remained clinically euthyroid. Thyroid function normalized after treatment cessation, confirming the transient nature of these alterations [55].

Collectively, these data suggest that ISO may induce mild, reversible, and clinically insignificant thyroid disturbances consistent with subclinical hypothyroidism. Periodic thyroid function testing (TFT) is recommended, particularly for patients with pre-existing thyroid disease or increased risk of hypothyroidism [54,55]

4.8. Neurological Adverse Effects of Isotretinoin

Neurological adverse effects related to ISO are uncommon but clinically relevant, most frequently presenting as headache, fatigue, or, rarely, intracranial hypertension. Retrospective data indicate that headache occurs in approximately 2–4% of patients, is typically mild, and resolves spontaneously without intervention [38]. Pseudotumor cerebri (idiopathic intracranial hypertension) has been described in rare cases, particularly among patients concurrently using tetracycline antibiotics. It manifests with persistent headache, papilledema, and transient visual disturbances, suggesting a pharmacodynamic interaction between ISO and tetracycline [38]. Additional symptoms such as dizziness, cognitive slowing, and muscle fatigue may occur but are generally reversible after dose reduction or discontinuation. No permanent neurological sequelae have been reported, and all patients recovered completely following drug withdrawal [48].

Overall, ISO-induced neurological events are rare, dose-dependent, and reversible. Persistent or severe headaches accompanied by visual changes warrant prompt evaluation to exclude intracranial hypertension. Concomitant use of tetracyclines should be avoided to minimize this risk [38,48].

4.9. Hematologic and Renal Adverse Effects of Isotretinoin

Hematologic and renal alterations observed during ISO therapy are generally mild, transient, and clinically insignificant. In a prospective study of 118 patients with moderate-to-severe acne, ISO administration resulted in fluctuations in platelet, leukocyte, and erythrocyte indices, all remaining within physiological ranges. Platelet and plateletcrit values increased transiently during the first month, then normalized, while white blood cell counts initially decreased and later returned to baseline, indicating a temporary modulation of bone marrow activity [56].

Ataseven and Bilgin reported a reduction in mean platelet volume (MPV) and platelet count in patients treated with ISO, possibly linked to interleukin-6–mediated effects on thrombopoiesis [57]**.** Reversible thrombocytopenia has also been observed and may result from bone marrow suppression, highlighting the need for individualized hematologic monitoring. Renal involvement is rare and usually mild. In a phase I trial evaluating the combination of ISO and vorinostat in patients with renal cell carcinoma, mild hematologic and renal abnormalities were the most common laboratory findings. Anemia (38%) was the predominant hematologic change, while renal parameters exhibited minimal and reversible deviations. No severe nephrotoxicity was observed [58].

In summary, ISO may cause mild, dose-dependent hematologic and renal fluctuations that are fully reversible. Routine laboratory monitoring is recommended, particularly in patients with comorbidities or concomitant nephrotoxic therapies [56-58].

4.10. Teratogenicity and Reproductive Safety of Isotretinoin

ISO is a potent teratogen capable of inducing severe and irreversible congenital malformations. Its teratogenicity results from excessive activation of RAR and RXR receptors during embryogenesis, disrupting the differentiation of neural, mesenchymal, and epithelial tissues and leading to profound structural anomalies [59].

A multicenter Turkish study involving nine pregnant women exposed to ISO demonstrated that pregnancy outcomes were strongly dependent on exposure timing. Three women underwent elective termination, while three who discontinued ISO prior to conception delivered healthy infants without malformations. The remaining cases resulted in early miscarriages or incomplete follow-up, confirming that teratogenic risk correlates with both dose and duration of exposure [60]. The same study highlighted ISO's prolonged elimination half-life and emphasized the importance of a washout period before conception. Strict contraceptive measures during and after treatment remain essential to prevent fetal exposure [60]. Regarding

paternal safety, ISO concentrations in seminal fluid were found to be negligible, far below teratogenic thresholds, confirming the absence of reproductive risk associated with paternal exposure [61].

In conclusion, ISO's teratogenic potential is confined to maternal exposure, while paternal use poses no reproductive hazard. Effective contraception, patient education, and post-treatment monitoring are essential to ensure reproductive safety and prevent adverse pregnancy outcomes [60,61].

5. Conclusions

ISO demonstrates unparalleled efficacy in the management of severe acne but exhibits a broad spectrum of dose-related systemic effects mediated by retinoid receptor signaling. Most adverse reactions are reversible, predictable, and reflect pharmacologic rather than toxic processes. With appropriate patient selection, dose optimization, and consistent biochemical and clinical monitoring, the risk–benefit ratio of ISO remains highly favorable. Clinicians should emphasize proactive management of mucocutaneous and metabolic effects, maintain vigilance for rare neurological or psychiatric events, and ensure strict reproductive safety measures. Future research should focus on elucidating molecular predictors of individual susceptibility and developing strategies that maintain ISO's therapeutic potency while minimizing systemic exposure and long-term risks

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Data and materials availability: All data sets collected during this study are available upon reasonable request from the corresponding author.

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