Supplementary Table S6. Overview of Reported Drugs Associated with Papilledema: Mechanism Classification

Drug	Therapeutic Category	Proposed Pathway	Primary Mechanism	Association Type
Doxycycline	Anti-infectives for systemic use	Intracranial hypertension	Impaired cerebrospinal fluid absorption at arachnoid granulations via disruption of cAMP-mediated transport pathways	Direct
Tetracycline	Anti-infectives for systemic use	Intracranial hypertension	Impaired cerebrospinal fluid absorption at arachnoid granulations via disruption of cAMP-mediated transport pathways	Direct
Minocycline	Anti-infectives for systemic use	Intracranial hypertension	Impaired cerebrospinal fluid absorption at arachnoid granulations with enhanced blood-brain barrier penetration due to high lipophilicity	Direct
Isotretinoin	Dermatologicals	Intracranial hypertension	Arachnoid villi lipid disruption and increased cerebrospinal fluid production via aquaporin expression changes in choroid plexus; contraindicated with tetracyclines due to synergistic risk	Direct
Somatotropin	Systemic hormonal preparations	Intracranial hypertension	Insulin-like growth factor 1–mediated increase in cerebrospinal fluid production at choroid plexus combined with sodium and water retention via the renin-angiotensin-aldosterone system	Direct
Cyclosporine	Antineoplastic and immunomodulating agents	Intracranial hypertension	Blood-brain barrier hyperpermeability via inhibition of adrenomedullin-mediated barrier function, P-glycoprotein efflux pump inhibition, endothelin-mediated vasoconstriction, and systemic hypertension	Direct
Dexamethasone	Systemic hormonal preparations	Intracranial hypertension (withdrawal-related)	Rebound increase in cerebrospinal fluid production upon drug withdrawal from hypothalamic-pituitary-adrenal axis suppression and relative adrenal insufficiency; occurs both after systemic and inhaled corticosteroid withdrawal	Indirect
Testosterone	Genitourinary system and sex hormones	Intracranial hypertension / cerebral venous sinus thrombosis	Dual mechanism: (1) androgen-mediated increase in cerebrospinal fluid secretion at choroid plexus, and (2) erythrocytosis-induced blood hyperviscosity predisposing to cerebral venous sinus thrombosis, both contributing to elevated intracranial pressure	Direct
Testosterone cypionate	Genitourinary system and sex hormones	Intracranial hypertension / cerebral venous sinus thrombosis	Same dual mechanism as testosterone: androgen-mediated cerebrospinal fluid secretion increase and erythrocytosis predisposing to cerebral venous sinus thrombosis	Direct
Cytarabine	Antineoplastic and immunomodulating agents	Intracranial hypertension and direct neurotoxicity	Intrathecal route: pseudotumor cerebri via disturbance of ATPase-dependent cerebrospinal fluid secretion; systemic route: DNA double-strand break–mediated neurotoxicity in postmitotic neurons (particularly Purkinje and Golgi cells)	Both
Imatinib	Antineoplastic and immunomodulating agents	Intracranial hypertension	Platelet-derived growth factor receptor inhibition leading to increased capillary permeability and fluid extravasation, resulting in cerebral edema; fluid retention reported in 74–84% of patients	Indirect
Nusinersen	Other medications	Intracranial hypertension	Intrathecal administration altering cerebrospinal fluid volume dynamics in patients with spinal muscular atrophy, a condition that independently predisposes to hydrocephalus and elevated intracranial pressure	Indirect
Amiodarone	Cardiovascular system	Direct optic nerve toxicity	Intracellular lipid lamellar body accumulation and phospholipidosis in optic nerve axons due to extreme lipophilicity (half-life up to 100 days), mechanically disrupting axoplasmic transport; produces disc edema with normal intracranial pressure	Direct
Sildenafil	Genitourinary system and sex hormones	Direct optic nerve toxicity	Non-arteritic anterior ischemic optic neuropathy from systemic hypotension in patients with structurally crowded optic disc anatomy (“disc at risk”); produces disc edema with normal intracranial pressure	Direct
Tacrolimus	Antineoplastic and immunomodulating agents	Direct optic nerve toxicity	Toxic optic neuropathy with direct endothelial injury, ischemic optic nerve damage, and demyelinating inflammation; funduscopy mimics papilledema but lumbar puncture shows normal intracranial pressure	Direct
Oxaliplatin	Antineoplastic and immunomodulating agents	Direct optic nerve toxicity	Extension of well-known peripheral neurotoxicity to optic nerve: acute toxicity via oxalate metabolite–mediated calcium chelation causing sodium channel dysfunction; chronic toxicity via cumulative DNA-platinum adduct formation and mitochondrial damage	Direct
Rituximab	Antineoplastic and immunomodulating	Immune-mediated (multifactorial)	Posterior reversible encephalopathy syndrome causing secondary intracranial pressure elevation from vasogenic brain edema; causality difficult to establish as nearly all reported cases involved	Indirect

Drug	Therapeutic Category	Proposed Pathway	Primary Mechanism	Association Type
	agents		patients on multiple immunosuppressants with hypertension and renal disease	
Levonorgestrel	Genitourinary system and sex hormones	Uncertain (hormonal)	Proposed hormonal modulation of choroid plexus function via progesterone receptors and weight gain; confounded by demographic overlap with the idiopathic intracranial hypertension population (young women of childbearing age)	Uncertain
Medroxyprogesterone acetate	Genitourinary system and sex hormones	Uncertain (hormonal)	Proposed weight gain and fluid retention mechanism; confounded by demographic overlap with the idiopathic intracranial hypertension population; the contribution of the exogenous hormone versus the underlying hormonal imbalance is difficult to disentangle	Uncertain
Anastrozole	Antineoplastic and immunomodulating agents	Uncertain (hormonal)	Hypothesized estrogen depletion creating relative androgen excess via aromatase inhibition, potentially driving androgen-mediated cerebrospinal fluid secretion increases; only two published case reports	Uncertain
Topiramate	Nervous system	Ocular toxicity (ciliochoroidal effusion syndrome)	Sulfonamide-derived idiosyncratic reaction causing increased permeability of ciliochoroidal vasculature, leading to fluid accumulation in the suprachoroidal space, ciliary body edema, forward rotation of the iris-lens diaphragm, secondary angle-closure glaucoma with acute elevation of intraocular pressure, and optic disc edema; persistent elevated intraocular pressure can cause permanent optic nerve damage	Direct

Note: Drugs classified under "Direct Optic Nerve Toxicity" cause optic disc edema that mimics papilledema on funduscopy but occurs with normal intracranial pressure on lumbar puncture, representing a fundamentally different pathology from true papilledema caused by elevated intracranial pressure. This distinction is clinically important: true papilledema requires neurological evaluation for elevated intracranial pressure, whereas drug-induced optic neuropathy requires drug cessation and ophthalmological management.