Drug-Induced Vestibular Toxicity and Ataxia:

A Vestibular Physician's Deep Review of Mechanisms, Monitoring, and Management

Vestibular Medicine for Vestibular Physicians

Central and Multisensory Vestibular Pathology — Module 4.6

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How to Use This Review

This literature review forms part of the Vestibular Medicine for Vestibular Physicians series published by the Australian Dizziness Clinics Education Hub. It is written for vestibular physicians, neuro-otologists, advanced ENT trainees, and vestibular physiotherapists working at the deep end of central and multisensory vestibular practice, where a working command of pharmacological mechanism, causality assessment, and atypical presentations is expected rather than optional.

The review is dense by design — intended as a 30–40 minute deep read or a desktop reference. It spans two linked clinical problems that share an iatrogenic origin: peripheral vestibulotoxicity, in which drugs destroy labyrinthine hair cells and produce bilateral vestibular hypofunction, and drug-induced ataxia, in which drugs impair the cerebellum and its connections. It is supported by an A4 clinician cheat sheet, short-form clinician videos, audio episodes, and a patient information leaflet within the same Education Hub module.

Callout Box Guide

□ **Key Point:** Foundational concepts and summary statements that anchor the core clinical content of each section.

□ **Clinical Insight:** Clinically relevant observations for direct application in assessment and management.

□ **Clinical Pearl:** High-yield memorable clinical points — the take-home messages most likely to change practice.

□ **Important:** Red flags, atypical presentations, and critical safety points requiring escalation or imaging.

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I. Introduction and Epidemiology

Drug-induced injury to the vestibular system and cerebellum is one of the few causes of progressive imbalance that is both common and, in large part, preventable [25,47]. It sits awkwardly across specialty boundaries — the offending drugs are prescribed by oncologists, intensivists, neurologists, psychiatrists and general practitioners, while the disability that follows lands in the vestibular clinic, often months or years later, stripped of its temporal link to the drug. This review treats the problem as a single clinical entity with two anatomical expressions: peripheral vestibulotoxicity, in which aminoglycosides, platinum agents and loop diuretics destroy or suppress labyrinthine hair cells, and central drug-induced ataxia, in which antiepileptics, lithium, metronidazole, cytotoxics and alcohol impair the cerebellum and its pathways [20,25,26].

True population incidence is unknown because the syndrome spans many drug classes and is chronically under-recognised; a systematic review of cerebellar adverse drug reactions concluded that reliable prevalence and incidence figures are still lacking for most agents [25]. What is clear is the burden carried by specific high-risk groups. Bilateral vestibular hypofunction (BVH) of any cause is estimated to affect roughly 28 per 100,000 adults, and ototoxic medication is one of its single largest identifiable causes — gentamicin alone accounts for a substantial share of acquired bilateral vestibular failure in tertiary case series [43,44]. In a 23-year Australian series of 103 patients with gentamicin vestibulotoxicity, the majority had received the drug at therapeutic serum levels with no documented overdose, underscoring that toxicity is frequently idiosyncratic rather than simply dose-dependent [7].

On the central side, antiepileptic drugs are the dominant contributors. Long-term phenytoin is associated with clinically detectable cerebellar ataxia in a sizeable minority of users, frequently accompanied by cerebellar atrophy on imaging [28,29]. Across drug classes, van Gaalen and colleagues identified more than ninety agents implicated in cerebellar ataxia, with antiepileptics, antineoplastics, lithium and certain antimicrobials carrying the strongest and most reproducible signals [25]. Platinum chemotherapy produces sensorineural hearing loss in 60–80% of treated children and vestibular dysfunction in an estimated 30–40%, a co-morbidity that compounds across the survivor's lifetime [13,14,46].

In the dizziness clinic itself, medication is a small but recoverable slice of the differential. Classic and contemporary surveys of dizzy patients attribute a few per cent of presentations to drugs or toxins, but the figure understates the clinical value of recognition: identifying a drug cause can spare invasive investigation and, where the injury is still reversible, restore function simply by stopping the agent [36]. The dominant epidemiological problem is attributional rather than numerical — the imbalance is real and persistent, but its iatrogenic origin is missed because the audiogram is normal, the drug was stopped long ago, or the symptoms are ascribed to the underlying illness [7,47].

□ **Key Point:** Drug-induced vestibular toxicity and ataxia is common in defined high-risk groups (intensive-care aminoglycoside exposure, platinum oncology, long-term antiepileptic therapy) and is frequently preventable. The diagnosis is missed far more often than it is made — usually because the link to the drug has been lost.

II. Pathophysiology — Ototoxic and Cerebellotoxic Mechanisms

The clinical syndromes converge on imbalance, but the lesions are anatomically and mechanistically distinct. Peripheral vestibulotoxins act on the sensory hair cells of the cristae and otolith organs; cerebellotoxins act on Purkinje cells and the vestibulocerebellum. A small number of agents — notably amiodarone and certain cytotoxics — straddle both compartments [25,34]. Figure 1 maps the principal drug classes onto their target organs and the syndromes they generate.

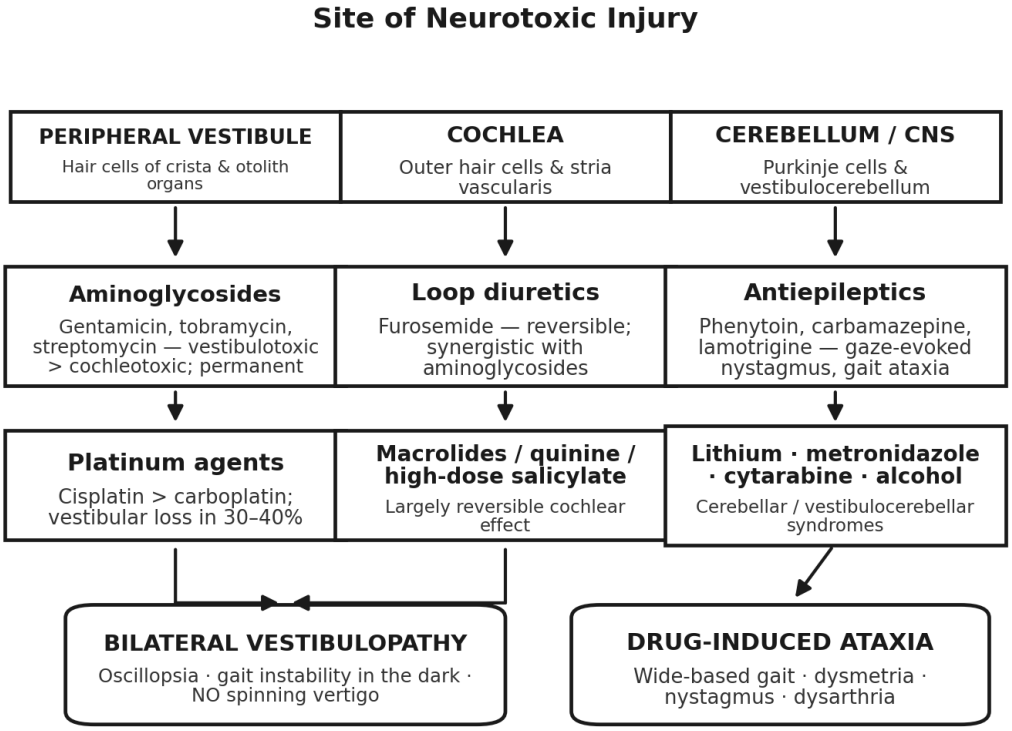

Figure 1. Site of neurotoxic injury — mapping the principal offending drug classes onto the peripheral vestibule, cochlea, and cerebellum, and the syndromes they produce.

Source: Adapted from Forge & Schacht [1], van Gaalen et al. [25], and Cianfrone et al. [20].

Aminoglycoside hair-cell injury

Aminoglycosides enter the hair cell through the apical mechanoelectrical transduction (MET) channel, a non-selective cation channel that is normally open at rest and is permeable to the drug molecule [1,2]. Once intracellular, the aminoglycoside chelates ferrous iron to form a redox-active complex that drives Fenton-type generation of reactive oxygen species — principally hydroxyl radical and superoxide [2,11]. The resulting oxidative load overwhelms endogenous antioxidant defences, triggers mitochondrial dysfunction and caspase-mediated apoptosis, and culminates in irreversible hair-cell death [1,2,6]. Figure 2 sets out the cascade in full.

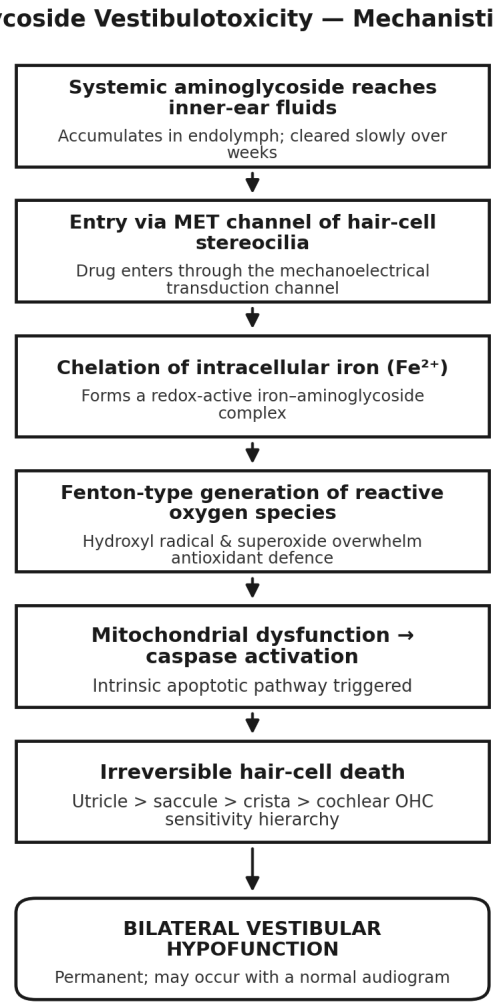

Figure 2. Aminoglycoside vestibulotoxicity — from MET-channel entry through iron chelation and reactive oxygen species to apoptotic hair-cell death and bilateral vestibular hypofunction.
Source: Adapted from Huth et al. [2] and Forge & Schacht [1].

Two features of this mechanism are decisive for the vestibular physician. First, susceptibility is hierarchical: utricular hair cells are more sensitive than saccular, which are more sensitive than the cristae, which are in turn more sensitive than cochlear outer hair cells at standard clinical doses [2,3]. This explains the central paradox of aminoglycoside toxicity — a patient can sustain profound bilateral vestibular loss with a completely normal audiogram. Second, gentamicin and streptomycin are preferentially vestibulotoxic, whereas amikacin, neomycin and kanamycin are preferentially cochleotoxic; tobramycin is intermediate [3,4,20]. The pharmacology of the specific agent therefore predicts the organ at risk.

Mitochondrial genotype modifies all of this. The m.1555A>G variant in the MT-RNR1 gene, which encodes the 12S ribosomal RNA, renders the mitochondrial ribosome structurally more bacterial-like and thus a higher-affinity target for aminoglycoside binding [11,12]. Carriers can develop rapid, profound, permanent hearing loss after a single standard dose, and because the trait is maternally inherited every matrilineal relative shares the risk [12]. This is the most clinically important pharmacogenomic variant in ototoxicity medicine and is addressed again under prevention.

Platinum and loop-diuretic mechanisms

Cisplatin generates reactive oxygen species in the stria vascularis and outer hair cells, forms platinum–DNA adducts that trigger apoptosis, and depletes glutathione, undermining antioxidant defence [5,16]. Damage begins at the basal turn of the cochlea, producing the characteristic high-frequency-first sensorineural loss, but the same oxidative mechanism injures the vestibular neuroepithelium, accounting for the 30–40% rate of vestibular involvement in treated patients [13,16,46]. Carboplatin is markedly less toxic, and oxaliplatin is largely spared, allowing rational substitution where oncological equivalence exists [16,48]. Loop diuretics act differently again: furosemide inhibits the Na–K–2Cl cotransporter of the stria vascularis, collapsing the endocochlear potential [20]. The effect is usually reversible in isolation, but the combination of a loop diuretic with an aminoglycoside is synergistically toxic and is one of the few genuinely avoidable iatrogenic catastrophes in inner-ear medicine [5,20].

Cerebellotoxic mechanisms

Drug-induced ataxia arises through several non-exclusive routes [25,26]. Direct neurotoxicity to Purkinje cells underlies the chronic phenytoin cerebellopathy, in which sodium-channel blockade is accompanied by Purkinje-cell loss, granule-cell depletion and Bergmann gliosis — the substrate of the cerebellar atrophy seen on imaging [27,28,29]. Physiological suppression, by contrast, is reversible: benzodiazepines and barbiturates potentiate GABAergic inhibition, and alcohol perturbs GABA and NMDA signalling, blunting cerebellar timing without necessarily destroying neurons — although chronic alcohol exposure does cause irreversible vermian degeneration [33]. Metabolic routes include valproate-induced hyperammonaemia, which produces an encephalopathy with prominent ataxia through astrocytic dysfunction rather than direct cerebellar action [25]. Immune-mediated injury is increasingly recognised with immune-checkpoint inhibitors, which can provoke an autoimmune cerebellitis [41]. Finally, vestibulocerebellar toxicity blends the two compartments: aminoglycoside-induced loss of peripheral vestibular input deprives the flocculonodular lobe of its afferent signal, producing an ataxic gait that is vestibular in origin but cerebellar in expression [8,9].

The cumulative-dose relationship for cisplatin deserves emphasis because it underwrites surveillance practice. Risk rises steeply above a cumulative dose of roughly 200 mg/m2, and the developing cochlea of the young child is more vulnerable than the adult organ, so the same milligram-per-square-metre exposure carries greater hazard the earlier it is delivered [13,46]. Cranial irradiation, renal impairment and concurrent aminoglycoside or loop diuretic exposure each shift the dose-response curve leftward, lowering the threshold at which clinically significant loss appears [5,16,46]. These potentiating factors are additive, and their coincidence in the critically ill or heavily pre-treated patient is precisely the situation in which the most severe injuries occur [20,45].

A mechanistic understanding also clarifies why the pattern of vestibular testing matters. Because the otolith organs and their afferents are injured early and disproportionately in aminoglycoside exposure, the cervical and ocular vestibular-evoked myogenic potentials frequently fall before the semicircular-canal VOR gain measured by the video head-impulse test declines, and well before any audiometric shift [2,17]. The canal paresis, when it comes, is bilateral and low-frequency, so the bithermal caloric response is the most sensitive canal measure and the rotatory chair the most specific for confirming symmetry of loss [10,24]. No single test is sufficient; the battery is interpreted as a whole against the drug history [10].

□ **Clinical Insight:** The single most useful mechanistic fact at the bedside is the hair-cell sensitivity hierarchy: utricle before saccule before crista before cochlea. It is why aminoglycoside vestibulotoxicity routinely coexists with a normal audiogram — and why audiometry alone can never exclude it.

III. The Major Offending Agents

Virtually any drug acting on the central nervous system or the inner ear can, at sufficient concentration, impair balance. The agents that matter clinically are those that combine appreciable risk with frequent use. Table 1 summarises the major classes by mechanism, target organ, and reversibility; the prose that follows highlights the features most relevant to vestibular practice [20,25].

Table 1. Principal drug classes causing vestibular toxicity and ataxia [3,13,20,25,29,30].

Drug class (examples)	Primary target	Mechanism	Reversibility
Aminoglycosides (gentamicin, streptomycin, tobramycin)	Vestibular hair cells > cochlea	MET-channel entry, iron–ROS, apoptosis	Permanent
Platinum agents (cisplatin > carboplatin)	Cochlea > vestibule	ROS, Pt–DNA adducts, glutathione depletion	Largely permanent
Loop diuretics (furosemide)	Stria vascularis	Na–K–2Cl cotransport inhibition	Usually reversible; synergistic with aminoglycosides
Antiepileptics (phenytoin, carbamazepine, lamotrigine)	Cerebellum	Na-channel block; chronic Purkinje-cell loss	Acute reversible; chronic may be permanent
Lithium	Cerebellum	Neurotoxic at high or even therapeutic levels	Usually reversible; SILENT syndrome permanent
Antimicrobials (metronidazole)	Dentate nuclei	Reversible oedema of dentate nuclei	Reversible on withdrawal
Cytotoxics (high-dose cytarabine, 5-FU)	Cerebellum	Direct cytotoxic Purkinje injury	Variable; may persist

Aminoglycosides

Gentamicin is the dominant vestibulotoxin in adult practice. The toxicity is classically delayed, emerging days to weeks after a course in intensive care or for endocarditis, frequently after the patient has been discharged and the drug forgotten [7,8]. The presentation is bilateral and symmetrical — oscillopsia and gait instability without spinning vertigo — and is therefore easily mistaken for deconditioning or generalised weakness in a recovering inpatient [8,9]. Risk is increased by prolonged courses, elevated troughs, renal impairment, concurrent loop diuretics, advanced age, and the m.1555A>G genotype, but a substantial minority of cases occur with impeccable serum levels [7,11]. Streptomycin shares this profile; topical aminoglycoside ear preparations applied to a perforated drum are an under-appreciated route of labyrinthine exposure [21].

Platinum agents

Cisplatin causes dose-dependent, cumulative, high-frequency sensorineural loss, with vestibular involvement in a large minority [13,16]. The vestibular deficit is usually silent during treatment, masked by the illness and by the cytotoxic and cranial-radiation co-exposures that frequently accompany it, and is revealed only by systematic testing [14,46]. Standardised grading using the SIOP Boston or Brock scales structures surveillance and triggers consideration of dose modification or otoprotection [13,15].

Antiepileptic drugs

Phenytoin is the archetype of central drug-induced ataxia. Acute toxicity produces gaze-evoked nystagmus and gait ataxia that track serum level; chronic exposure can produce a fixed cerebellar syndrome with radiological atrophy that correlates more closely with cumulative phenytoin burden than with seizure frequency [27,28,29]. Carbamazepine and oxcarbazepine commonly cause level-dependent imbalance, diplopia and vertigo, and lamotrigine in overdose can produce downbeat nystagmus and ataxia [25]. Switching to a non-cerebellotoxic agent such as levetiracetam is the preferred route where the epilepsy permits [25].

Lithium, antimicrobials, cytotoxics and others

Lithium produces the classic triad of tremor, ataxia and confusion, and can be neurotoxic even at therapeutic levels, particularly when renal clearance falls or sodium is depleted [25,30]. Most episodes resolve, but the syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) describes persistent cerebellar dysfunction after severe toxicity [30]. Metronidazole causes a reversible cerebellar syndrome with symmetric T2-hyperintense lesions of the dentate nuclei that resolve on withdrawal [31]. High-dose cytarabine produces an acute cerebellar syndrome — dysarthria, nystagmus and truncal ataxia within days of infusion — that may not fully reverse [32]. Amiodarone is a useful reminder that a single drug can

be both peripheral and central, having been reported to cause nystagmus, ataxia and vestibular suppression [34]. Alcohol remains the most prevalent cerebellotoxin worldwide, causing both acute intoxication ataxia and chronic vermian degeneration [33].

Beyond these headline classes, a long tail of agents contributes to imbalance in everyday prescribing and is easily overlooked. Benzodiazepines, barbiturates and the non-benzodiazepine hypnotics produce dose-dependent central depression that blunts cerebellar timing and, in the older patient on polypharmacy, tips a marginal balance system into overt instability and falls [25]. First-generation antihistamines, tricyclic antidepressants, baclofen and several anticonvulsant adjuncts act similarly. Vancomycin alone is modestly ototoxic but potentiates aminoglycoside injury when the two are combined in sepsis, so therapeutic drug monitoring of both agents is standard when they are co-administered [5,20]. Quinine and high-dose salicylates cause a reversible cochlear effect with tinnitus, and topical aminoglycoside ear preparations applied across a perforated drum can reach the labyrinth directly — a route prescribers rarely regard as systemic [20,21]. The practical lesson is that the medication review must be exhaustive rather than confined to the obvious culprits [24,25].

□ **Important:** The combination of an aminoglycoside and a loop diuretic is synergistically ototoxic and must be avoided where clinically possible. If both are unavoidable, separate administration, monitor therapeutic drug levels for both, and undertake formal audiological and vestibular surveillance from the first dose.

IV. Clinical Features and the Peripheral–Central Divide

The clinical task is to recognise that imbalance is drug-related and then to localise it — peripheral vestibulotoxic, central cerebellotoxic, or both. The two patterns are separable at the bedside, and the distinction directs investigation and rehabilitation. Figure 3 sets out the reasoning.

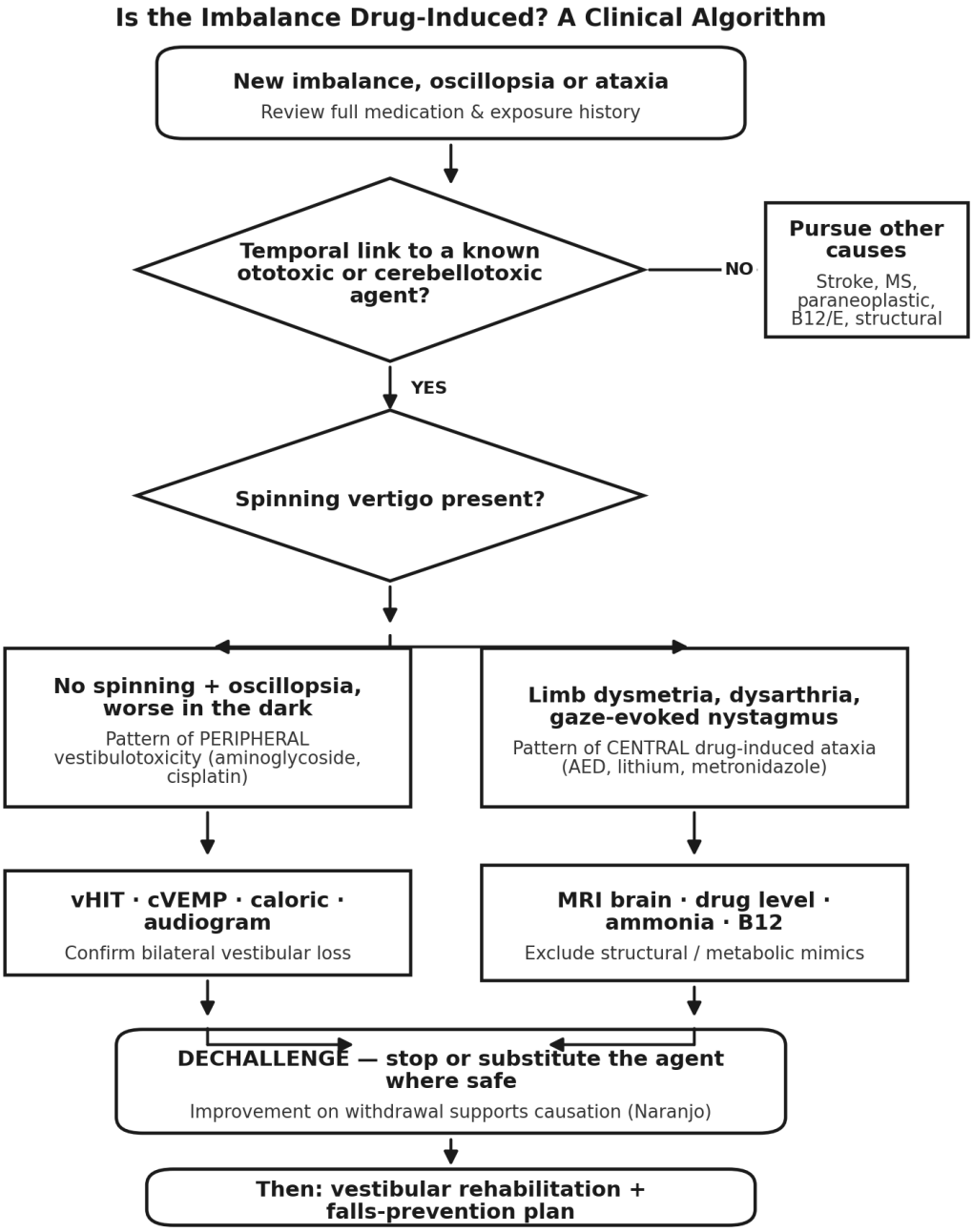

Figure 3. A clinical algorithm for establishing whether new imbalance is drug-induced and localising it to the peripheral vestibule or the cerebellum.

Source: Adapted from Strupp et al. [10] and van Gaalen et al. [25].

The peripheral pattern — bilateral vestibular hypofunction

Because both labyrinths are damaged symmetrically, there is no asymmetric vestibular signal and therefore no spinning vertigo — the cardinal negative feature that so often misleads the unwary [10,37]. Instead the patient describes a triad: oscillopsia (the visual scene bouncing or blurring with head movement, from failure of the vestibulo-ocular reflex), postural instability that is dramatically worse in the dark and on uneven or compliant surfaces, and a cognitive 'fog' or fatigue on movement [10,43]. Bedside signs include a bilaterally abnormal head-impulse test with overt corrective saccades, a markedly positive Romberg in the dark, and inability to maintain visual acuity during passive head oscillation (a positive dynamic visual acuity test) [10,38]. In infants the same lesion presents as delayed independent walking and a wide-based gait [14].

The central pattern — drug-induced ataxia

Cerebellar drug toxicity produces the familiar syndrome of wide-based gait, limb dysmetria, dysdiadochokinesis, intention tremor, scanning dysarthria and gaze-evoked nystagmus [25,26]. A defining feature is the temporal profile: symptoms evolve subacutely over days to weeks after a new drug or a dose increase, distinguishing them from the abrupt onset of stroke and the slow march of degenerative ataxia [25]. The deficit is usually 'pure' cerebellar, with preserved strength, sensation and cognition, unless the drug is also producing a global encephalopathy (valproate, lithium) or a peripheral neuropathy (platinum, metronidazole), in which case sensory ataxia and a positive Romberg in the light may be superimposed [25,26]. Downbeat nystagmus is a useful pointer to lithium or lamotrigine, and to floccular involvement generally [25].

□ **Clinical Pearl:** Ask one screening question of every patient with unexplained imbalance: 'Does the world bounce or blur when you walk or move your head?' A yes, without spinning vertigo, points hard at bilateral vestibular hypofunction — the silent signature of aminoglycoside and platinum vestibulotoxicity.

V. Diagnostic Criteria and Causality Assessment

There are no formal consensus diagnostic criteria for drug-induced vestibular toxicity or ataxia equivalent to those for Ménière's disease or vestibular migraine. Diagnosis is a structured clinical judgement built on four pillars [25]: a documented exposure to an agent known to be ototoxic or cerebellotoxic, with timing that precedes symptom onset; a clinical syndrome consistent with peripheral vestibular or cerebellar dysfunction; reasonable exclusion of alternative causes; and improvement after withdrawal of the suspected drug (dechallenge). Where bilateral vestibulopathy is the expression, the Bárány Society diagnostic criteria provide a rigorous peripheral framework — bilaterally reduced or absent VOR function confirmed by head-impulse testing, caloric testing or the rotatory chair — onto which the drug history is mapped [10].

Formal causality instruments add objectivity. The Naranjo Adverse Drug Reaction Probability Scale scores the temporal relationship, the presence of alternative explanations, the response to dechallenge and (rarely) rechallenge, and supportive evidence such as a toxic drug level, classifying the association as doubtful, possible, probable or definite [35]. Dechallenge is the single most informative step: resolution of metronidazole ataxia or stabilisation of cerebellar signs after stopping phenytoin strongly implicates the drug [25,31]. Deliberate rechallenge, although diagnostically definitive, is rarely ethical and should not be undertaken to confirm a vestibulotoxic diagnosis [35]. Supportive findings include a supratherapeutic phenytoin or lithium level, and characteristic imaging — symmetric dentate-nucleus signal change in metronidazole toxicity, or cerebellar atrophy in chronic phenytoin exposure [28,29,31].

□ **Clinical Insight:** Causality in drug-induced ataxia is established prospectively, not retrospectively: the cleanest proof is improvement on dechallenge. Where the drug is essential and cannot be stopped, document the Naranjo score, the drug level, and the imaging — the diagnosis then rests on convergent evidence rather than a single test.

VI. Investigations and Monitoring

Investigation serves two purposes: to localise and quantify the deficit, and to exclude the mimics that share its presentation. Vestibular function testing anchors the peripheral assessment. The video head-impulse test (vHIT) quantifies semicircular-canal VOR gain and detects the corrective saccades of bilateral hypofunction; bithermal caloric testing provides a quantitative, side-specific measure of low-frequency canal function; and cervical and ocular vestibular-evoked myogenic potentials (cVEMP, oVEMP) interrogate otolith and inferior- and superior-nerve pathways [10,17]. cVEMP amplitude reduction can precede audiometric change in aminoglycoside exposure and is among the earliest detectable markers of vestibulotoxicity [17].

Audiological assessment runs in parallel because the cochlea and labyrinth are injured together. High-frequency audiometry (above 8 kHz) and distortion-product otoacoustic emissions detect outer-hair-cell loss before conventional pure-tone audiometry shifts, making them the most sensitive early cochlear

markers [22]. For the central pattern, MRI of the brain is essential to exclude structural and demyelinating disease and may show cerebellar atrophy or the dentate changes of metronidazole toxicity; serum drug levels, ammonia, vitamin B12 and E, thyroid and renal function complete the metabolic screen [25,29,31]. Figure 4 and Table 2 set out a surveillance pathway for patients receiving ototoxic drugs.

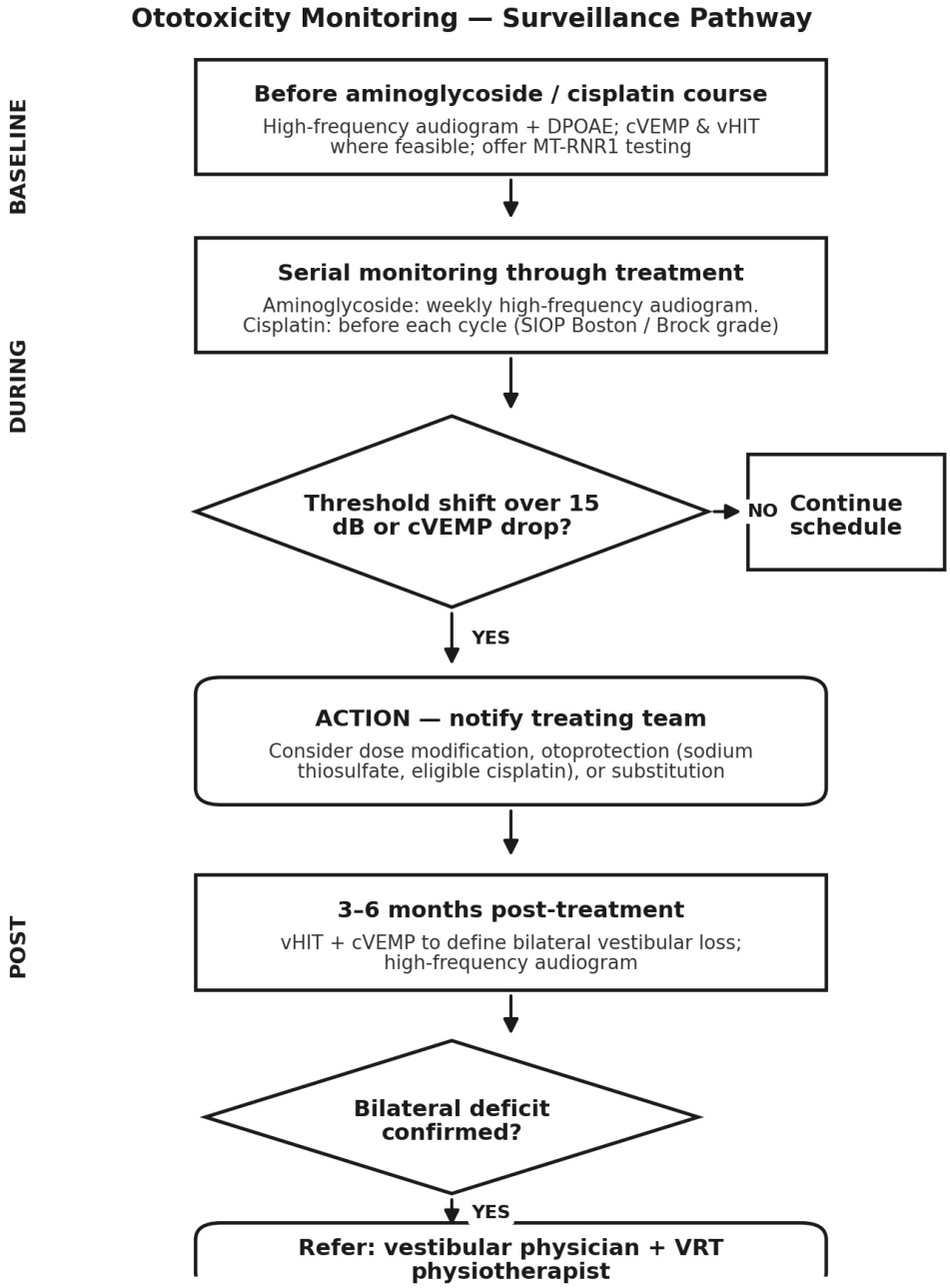

Figure 4. Ototoxicity surveillance pathway — baseline, on-treatment, and post-treatment audiological and vestibular monitoring, with action thresholds.

Source: Adapted from American Speech-Language-Hearing Association guidance [23] and Konrad-Martin et al. [22].

Table 2. Ototoxicity monitoring protocol by phase [17,22,23].

Phase	Assessment	Action threshold
Baseline (pre-treatment)	High-frequency audiogram + DPOAE; cVEMP and vHIT where feasible	Establish reference; identify pre-existing loss
During aminoglycoside therapy	High-frequency audiogram (weekly where feasible)	Threshold shift over 15 dB triggers review
During cisplatin therapy	Audiogram before each cycle; SIOP Boston / Brock grade	Grade 2 prompts regimen / otoprotection review

Post-treatment (3–6 months)	vHIT + cVEMP; high-frequency audiogram	Confirmed bilateral loss: refer for rehabilitation

Interpreting the battery requires holding the expected drug-specific pattern in mind. Aminoglycoside vestibulotoxicity yields bilaterally reduced vHIT gain with overt and covert corrective saccades, bilaterally depressed or absent caloric responses, and reduced or absent VEMPs, against a backdrop of a normal or near-normal standard audiogram [8,10,17]. Cisplatin, by contrast, produces a high-frequency sensorineural audiogram first, with vestibular abnormality emerging later and in a minority [13,16]. In suspected central drug-induced ataxia the vestibular battery is frequently normal, and the diagnostic weight falls on MRI, serum drug levels and the metabolic screen, with the imaging serving chiefly to exclude a structural or demyelinating mimic rather than to confirm the drug effect [25,29]. A normal MRI does not exclude reversible cerebellotoxicity, and a single supratherapeutic level, while supportive, is neither necessary nor sufficient on its own [25,35].

□ **Clinical Pearl:** Audiometry alone is inadequate ototoxicity surveillance. Pair high-frequency audiometry with cVEMP and vHIT — the vestibular markers move first in aminoglycoside exposure, and a falling cVEMP amplitude is an early warning to review the regimen while function can still be protected.

VII. Differential Diagnosis

The differential divides along the same peripheral–central axis. For the bilateral-vestibulopathy presentation, the alternatives include idiopathic and genetic bilateral vestibulopathy, CANVA (cerebellar ataxia with neuropathy and vestibular areflexia), neurosarcoidosis, autoimmune inner-ear disease and sequential bilateral vestibular neuritis [10,43]. For the cerebellar presentation, the field is broader still — acute cerebellar stroke, paraneoplastic and autoimmune cerebellar degeneration, hereditary and sporadic ataxias, vitamin-deficiency syndromes (notably Wernicke's encephalopathy and B12 deficiency), multiple sclerosis, and structural posterior-fossa lesions [25,26,42]. Table 3 distils the features that most efficiently separate drug-induced disease from its principal mimics.

Table 3. Differentiating drug-induced disease from key mimics [10,25,26,42].

Condition	Discriminating features	Decisive test
Drug-induced (this review)	Temporal link to agent; improves on dechallenge	Drug history + Naranjo; dechallenge
Cerebellar stroke	Hyperacute onset; focal signs; vascular risk	MRI-DWI
Paraneoplastic / autoimmune cerebellitis	Subacute; no drug link; antibody-positive	Onconeural / GAD antibodies, CSF
Wernicke's encephalopathy	Ataxia, ophthalmoplegia, confusion; at-risk host	Thiamine trial; MRI mammillary bodies
Idiopathic bilateral vestibulopathy / CANVA	No ototoxic exposure; sensory neuropathy in CANVA	vHIT/caloric + RFC1 testing

VIII. Management, Otoprotection and Prevention

Because most established hair-cell and Purkinje-cell injury is irreversible, the highest-value interventions are preventive and the second-highest are early. Management has three arms: stopping or modifying the offending agent, protecting the inner ear where the drug is unavoidable, and rehabilitating the resulting deficit [25,38,47]. Figure 5 sets out the pathway from confirmed toxicity to functional adaptation.

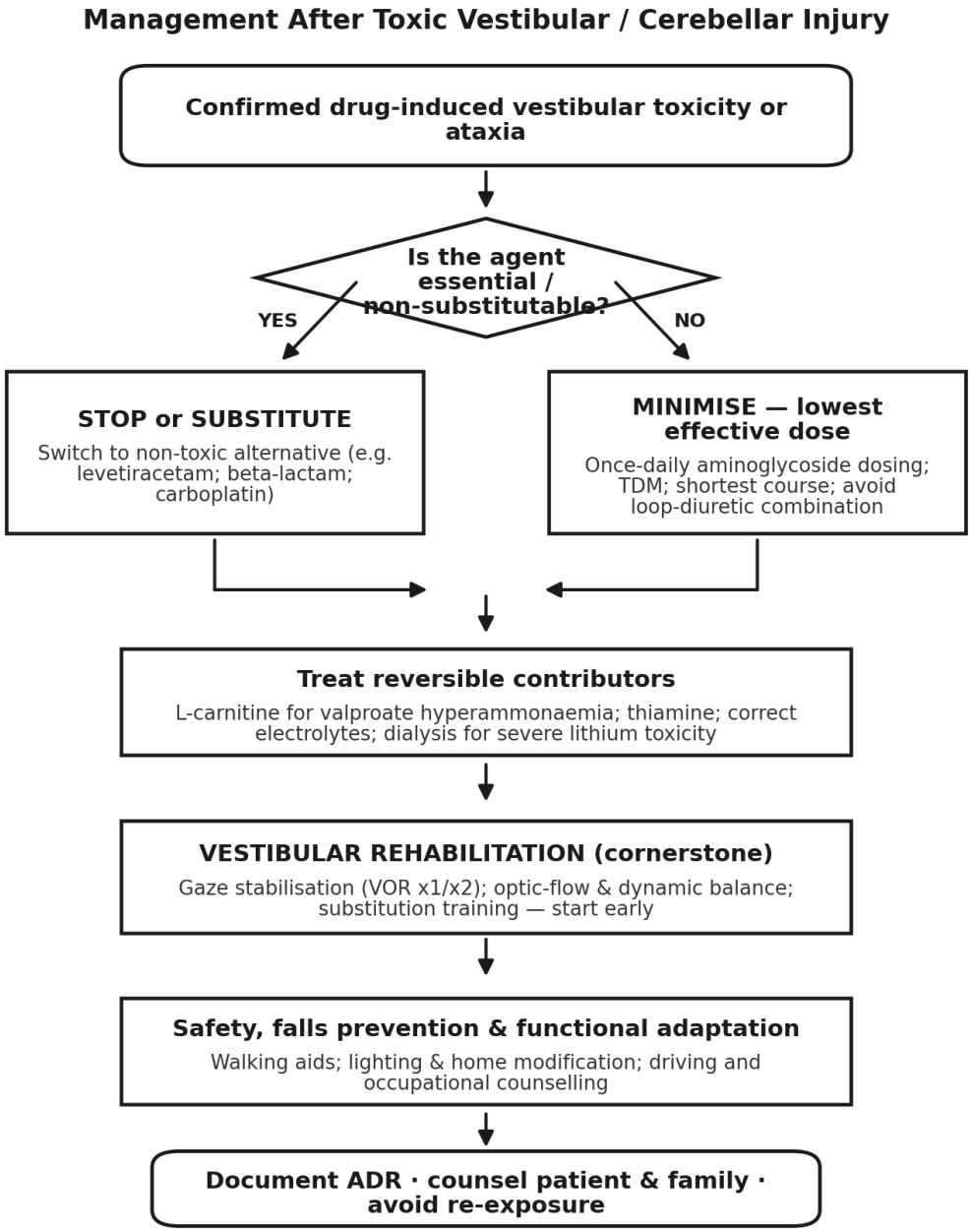

Figure 5. Management pathway after confirmed drug-induced vestibular toxicity or ataxia — from drug modification through reversible-contributor treatment to vestibular rehabilitation and safety planning.
Source: Adapted from van Gaalen et al. [25] and Hall et al. [38].

Drug modification

Discontinuation, where safe, is the primary intervention, and for reversible toxins — metronidazole, loop diuretics, benzodiazepines — it is frequently curative [25,31]. Where the drug is essential, the decision becomes a risk–benefit calculation: substitute a less-toxic congener (carboplatin for cisplatin, levetiracetam for phenytoin), reduce the dose, or accept the toxicity when the indication is life-saving [16,25]. Reversible metabolic contributors should be corrected in parallel — L-carnitine for valproate hyperammonaemia, thiamine for at-risk patients, electrolyte correction, and haemodialysis for severe lithium toxicity [25,30].

Otoprotection and aminoglycoside stewardship

For aminoglycosides, stewardship is protection: once-daily extended-interval dosing produces lower sustained inner-ear concentrations than divided dosing while preserving bactericidal efficacy, therapeutic

drug monitoring (preferably AUC-based) limits accumulation, and duration minimisation reduces cumulative exposure [1,5]. Beta-lactams and inhaled non-aminoglycoside agents offer alternatives in many settings [20]. For cisplatin, sodium thiosulfate is the first otoprotectant with high-quality randomised evidence: the SIOPEL 6 trial and the COG ACCL0431 trial both demonstrated significant reduction in cisplatin-induced hearing loss when sodium thiosulfate was given six hours after cisplatin in children with localised disease, although its use must be timed to avoid blunting antitumour effect in disseminated malignancy [18,19].

Prevention is sharpened by stratifying the individual patient's risk before exposure. The multipliers that matter are well characterised and, importantly, several are modifiable [20,46]. Table 5 sets out the principal risk factors and the practical mitigation for each. Identifying a high-risk host — the renally impaired neonate, the heavily pre-treated oncology patient, the matrilineal relative of a known m.1555A>G carrier — converts a generic warning into a specific, actionable plan [11,45].

Table 4. Risk multipliers for drug-induced inner-ear and cerebellar injury, and mitigation [11,20,24,45,46].

Risk factor	Mitigation
Cumulative aminoglycoside / cisplatin dose	Track cumulative dose; shortest effective course; substitution above threshold
m.1555A>G (MT-RNR1) genotype	Point-of-care testing before planned non-emergency aminoglycosides; avoid if positive
Renal impairment	Dose-adjust; therapeutic drug monitoring; avoid nephrotoxic combinations
Concurrent loop diuretic with aminoglycoside	Avoid co-administration; separate dosing; intensive monitoring
Young age / developing inner ear	Heightened surveillance; favour otoprotection and less-toxic congeners
Polypharmacy in the older adult	Rationalise sedatives and anticholinergics; falls assessment

Genetic prevention

MT-RNR1 m.1555A>G testing converts a catastrophic, irreversible injury into an avoidable one. Point-of-care testing now returns a result within hours from a cheek swab, at a fraction of the cost of the deafness it prevents [11,12]. In non-emergency settings where aminoglycoside therapy is planned, testing should be offered; a positive result mandates avoidance where any equivalent alternative exists, and — because the trait is maternally inherited — counselling of the wider matrilineal family [11,12].

□ **Key Point:** Prevention dominates the value hierarchy: aminoglycoside stewardship, MT-RNR1 testing before planned non-emergency courses, avoidance of the loop-diuretic combination, cisplatin otoprotection where eligible, and early vestibular rehabilitation together prevent far more disability than any treatment applied after the fact.

IX. Rehabilitation, Prognosis and Special Populations

Where vestibular hair cells have died, there is no recovery of peripheral function, and management pivots entirely to central compensation through vision and somatosensation [38]. Vestibular rehabilitation is the cornerstone and is supported by a clinical practice guideline that grades the evidence as strong: gaze-stabilisation exercises (VOR x1 and x2) train any residual vestibular response and recruit visual substitution; optic-flow and dynamic-balance training recalibrate the visual–vestibular interaction; and progressive balance work on compliant and uneven surfaces, with and without vision, builds somatosensory substitution [38,39]. For pure cerebellar drug-induced ataxia, coordinative and balance-focused physiotherapy similarly improves function, and timing matters in both: earlier intervention exploits a wider window of neural plasticity [38,40].

Prognosis is determined by mechanism. Reversible toxins recover predictably — short-acting sedatives within days, metronidazole within weeks of withdrawal — whereas agents that kill cells (aminoglycosides, cisplatin) or produce chronic atrophy (phenytoin, alcohol) leave permanent deficits [25,31,32]. Recovery is functional rather than anatomical: patients frequently compensate well despite a persistently abnormal vHIT or residual cerebellar atrophy [28]. Relapse is essentially a function of re-exposure, which is almost entirely avoidable; a patient who developed ataxia on carbamazepine or vestibulotoxicity on gentamicin should avoid that agent for life, and in the case of m.1555A>G the prohibition extends across the maternal family [12,30]. Table 4 summarises reversibility by agent.

Table 5. Reversibility and prognosis by agent [9,25,30,31,32].

Agent	Typical course	Residual risk
Benzodiazepines, antihistamines	Resolves within days of clearance	Minimal
Metronidazole	Resolves within weeks of withdrawal	Low
Lithium	Usually reversible	SILENT syndrome if severe toxicity
Phenytoin (chronic)	Partial recovery over months	Permanent atrophy in a subset
Aminoglycosides, cisplatin	No peripheral recovery	Permanent bilateral vestibular loss

Special populations deserve explicit attention. Neonates and infants exposed to aminoglycosides in intensive care, and children receiving platinum chemotherapy, may present years later with delayed motor milestones and balance failure rather than a vestibular complaint, and their plasticity makes early rehabilitation especially valuable [14,46]. Older adults on polypharmacy accumulate additive risk and are the group in whom drug-induced imbalance is most often mislabelled as multifactorial age-related instability [25]. The pregnant or renally-impaired patient has altered drug handling that lowers the toxic threshold for lithium and aminoglycosides alike [30].

Counselling closes the loop. Patients are often relieved to learn that their imbalance has a reversible or at least explicable cause, and adherence to drug avoidance is correspondingly high once the link is understood [25,30]. The conversation should be explicit about what to expect: that peripheral vestibular loss will not recover but that the brain will, over weeks to months, learn to substitute vision and proprioception; that progress depends on consistent rehabilitation; and that certain environments — darkness, water, uneven ground — will remain disproportionately challenging and warrant practical adaptation [38,39]. Where a genetic susceptibility has been identified, the duty extends to the family, and a documented alert in the medical record guards against inadvertent re-exposure during a future emergency [11,12].

□ **Important:** Vestibular rehabilitation should begin as soon as the diagnosis is made. The window for effective central compensation is widest early and narrows with time and age — every month of undiagnosed bilateral vestibular loss is a month of compensation foregone.

X. Guidelines, Controversies and Future Directions

Guidance is fragmented across the contributing specialties. Ototoxicity-monitoring frameworks exist from audiological and oncology bodies, the Bárány Society defines bilateral vestibulopathy, and the vestibular rehabilitation guideline governs treatment, but no single document integrates the pharmacological, vestibular and rehabilitative strands into one pathway — a gap this review is intended to bridge [10,23,38]. Several questions remain genuinely contested.

The first is the balance between under-recognition and over-attribution. Because no confirmatory test exists, diagnosis rests on judgement, and clinicians err in both directions — missing gentamicin vestibulotoxicity for years on one hand, and anchoring prematurely on a drug while a tumour or paraneoplastic process is overlooked on the other [25]. Structured causality scoring mitigates but does not eliminate the problem [35]. The second is the reach of pharmacogenomic screening: m.1555A>G testing before planned aminoglycoside therapy is cost-effective and increasingly feasible, yet it is not embedded in most prescribing pathways [11,12]. The third is therapeutic — whether persistent ataxia,

regardless of cause, warrants symptomatic pharmacotherapy. Agents such as 4-aminopyridine for downbeat nystagmus and a handful of drugs trialled in degenerative ataxia have modest evidence, but none is established for drug-induced disease, where removal of the cause and rehabilitation remain the cornerstones [40].

The most promising future direction is targeted otoprotection. Antioxidants, iron chelators, and inhibitors of the apoptotic cascade have strong preclinical rationale against aminoglycoside and cisplatin injury, and sodium thiosulfate has already crossed into clinical practice for selected cisplatin protocols [6,18,19]. Hair-cell regeneration through Atoh1 and Wnt-pathway manipulation, and immunomodulation for checkpoint-inhibitor cerebellitis, are earlier in development but point toward a future in which iatrogenic vestibular injury is not merely prevented but repaired [6,41,47]. Until then, the vestibular physician's leverage lies in vigilance: a drug history taken in every case of unexplained imbalance, surveillance that pairs vestibular with audiological testing, and rehabilitation begun without delay.

□ **Clinical Pearl:** If you remember one thing from this review: take a drug history in every patient with unexplained imbalance, and test the vestibular system — not just hearing — in everyone exposed to an aminoglycoside or cisplatin. The diagnosis you make today is the disability you prevent, or the compensation you start, tomorrow.

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