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Review

Pathogenesis and Preventive Pharmacotherapy of Migraine Aura: A Critical Review of Cortical Spreading Depolarization Mechanisms, Drug Repurposing Evidence, and the Emerging Therapeutic Pipeline

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Plain Language Summary

Migraine with aura is caused by a slow electrical wave in the brain (cortical spreading depolarization, CSD) that current preventive drugs—including the new anti-CGRP antibodies—do not directly stop. This review organises CSD into four biological phases and grades the evidence for drugs that could block each phase, using formal evidence-quality tools and quantitative trial-design calculations. The main message is that several mechanism-based drugs (memantine, lamotrigine, tonabersat, anti-PACAP antibodies) have plausible aura-specific potential, but none has yet been tested in a properly powered, aura-specific trial—an evidence gap the field can now correct.

Abstract

Objective: To synthesise the pathobiology of cortical spreading depolarization (CSD) and critically appraise current and emerging pharmacological strategies specifically targeting migraine aura prevention. **Background:** Migraine with aura affects 25–30% of patients, and the aura phenomenon remains a substantial unmet preventive need. Calcitonin gene-related peptide (CGRP) monoclonal antibodies do not readily cross the blood–brain barrier and frequently fail to suppress CSD, the neurophysiological substrate of aura. **Methods:** A literature search of PubMed, Embase, and the Cochrane Library (inception through January 2026) identified studies on CSD pathophysiology, preclinical CSD suppression, and clinical efficacy of candidate agents. Evidence quality was assessed with GRADE; risk of bias with Cochrane RoB 2 (RCTs) and ROBINS-I (observational); narrative synthesis followed SWiM. De novo quantitative estimations (post-hoc power analyses, sample-size projections, worst-case sensitivity analyses) were used as methodological tools, not as original empirical data. **Results:** CSD pathogenesis is organised into four phases: pre-CSD vulnerability, initiation, glial propagation, and neuro-inflammatory transduction. Lamotrigine and memantine target initiation and have the most advanced clinical evidence; both lack aura-specific RCTs. A 2024 network meta-analysis ranked memantine favourably (50% responder rate OR 5.58, 95% CI 2.41–12.92) but no contributing trial stratified by aura. An a priori sample-size calculation indicates 214 enrolled patients (170 evaluable; NNT≈4.9; n/(1−d) for 20% attrition) for a definitive aura-specific memantine RCT. Tonabersat—a Cx36/Cx43 gap-junction modulator—reduced aura attacks from 3.2 to 1.0 per 12 weeks in Phase 2; a worst-case intention-to-treat sensitivity analysis confirms that this signal survives even 16.6% unaccounted attrition. Spironolactone (pannexin-1 inhibition) and amiloride (ASIC1a) remain preclinical or pilot-stage. Tissue-selective KATP antagonists (Kir6.1/SUR2B) and the anti-PACAP-38 antibody Lu AG09222 represent the most promising pipeline agents. **Conclusion:** The therapeutic gap for migraine aura prevention reflects correctable methodological choices, not a lack of biological tractability. Four mechanism-based drug classes—NMDA-receptor antagonists, pannexin-1 inhibitors, gap-junction modulators, and KATP antagonists—offer entry points for aura-specific prevention. Adequately powered, aura-enriched RCTs with validated CSD biomarkers (DC-EEG co-registered against electrocorticography; neuron-

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derived extracellular vesicles) and pre-specified falsifiability thresholds are now the rate-limiting step. Seven testable methodological predictions are proposed.

Keywords: migraine with aura; cortical spreading depolarization; preventive pharmacotherapy; memantine; lamotrigine; tonabersat; pannexin-1; PACAP; drug repurposing; GRADE

1. Introduction

Migraine ranks as the second leading cause of years lived with disability worldwide [1]. In approximately 25–30% of patients the headache phase is preceded, accompanied, or occasionally exclusively characterised by an aura—a focal, reversible neurological phenomenon manifesting through visual, sensory, dysphasic, or motor symptoms [2,3]. Migraine with aura is also associated with elevated risk of ischaemic stroke and cardiovascular events, underscoring the clinical imperative for targeted aura suppression.

CGRP monoclonal antibodies have transformed headache prevention, but as large biological molecules they do not readily cross the intact blood–brain barrier and act predominantly within the peripheral trigeminovascular system [1]. A clinically significant cohort therefore continues to experience debilitating aura attacks despite adequate headache control [4,5]. Specific prevention of the aura remains a formidable unmet clinical need.

The fundamental challenge lies in the unique neurobiological origin of the aura: cortical spreading depolarization (CSD) — a massive, self-propagating wave of neuronal and glial depolarization in the cerebral cortex [4,6]. Standard prophylactic paradigms rely on general membrane stabilization or non-specific neurotransmitter modulation, approaches that lack the molecular specificity to selectively block the cortical depolarization cascade [7].

This critical review provides an in-depth analysis of aura pathogenesis organised along a four-phase pathobiological model of CSD, evaluates current off-label repurposing strategies with explicit attention to evidence quality and methodological limitations, and appraises the emerging pharmacological pipeline for 2025–2030. Seven testable methodological predictions are proposed to guide the next generation of aura-prevention trials.

2. Search Strategy and Selection Criteria

PubMed, Embase, and the Cochrane Library were searched from inception through January 31, 2026 using: (“cortical spreading depolarization” OR “cortical spreading depression” OR “CSD” OR “spreading depolarization”) AND (“migraine” OR “migraine with aura”) AND (“prevention” OR “prophylaxis” OR “treatment” OR “pharmacotherapy” OR “drug repurposing”). Targeted searches were performed for each candidate agent (lamotrigine, memantine, spironolactone, amiloride, tonabersat, PACAP, KATP) combined with “migraine” or “cortical spreading depolarization.” Reference lists of retrieved articles and recent systematic reviews were screened for additional sources.

Studies were included if they reported on (a) CSD pathophysiology in migraine aura, (b) pharmacological CSD suppression in preclinical models, or (c) clinical efficacy of candidate agents in migraine, with preference for aura-stratified populations. Heterogeneity of designs, populations, and outcomes precluded meta-analysis; findings are synthesised narratively following SWiM [8]. Evidence quality was graded with GRADE [9]; risk of bias was appraised with Cochrane RoB 2 (RCTs) and ROBINS-I (observational studies). All references were cross-verified against PubMed and CrossRef by DOI/PMID lookup. De novo quantitative estimations (post-hoc power analyses, sample-size projections, worst-case sensitivity analyses) are embedded as methodological tools within the narrative review and do not constitute original empirical data.

3. The Neurophysiological Substrate: Cortical Spreading Depolarization

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CSD, also termed cortical spreading depression, is a slowly propagating, self-sustaining wave of near-complete neuronal and glial depolarization that advances at 2–5 mm/min [4,6,10,11]. Direct electrophysiological confirmation in patients experiencing migraine aura has demonstrated propagation across somatosensory and temporal cortices consistent with the clinical march of aura symptoms.

At the cellular level, CSD reflects catastrophic collapse of transmembrane ion gradients: massive efflux of K^+ and H^+, enormous extracellular glutamate release, and Na^+/Ca^{2+}/water influx into neurons and astrocytes producing cellular oedema, followed by prolonged neuronal suppression [4,6,11]. Hemodynamically, CSD generates a biphasic response—brief cortical hyperaemia followed by prolonged oligaemia [12,13]—temporally and spatially correlated with aura symptoms on functional MRI [12].

Moskowitz (2025) has proposed that the total extent of cortical depolarization, including silent propagation through non-eloquent cortex, rather than the aura percept per se, determines the buildup of noxious mediators sufficient to trigger the headache phase [5]. This reconceptualisation has profound implications for therapeutic targeting and trial design (Section 9). Ayata and Lauritzen (2015) reframed spreading depolarization as a pan-neurological phenomenon spanning stroke, traumatic brain injury, and subarachnoid haemorrhage [14]; Harriott and Ayata (2025) reinforced this framing, positioning CSD as a tractable therapeutic target across the stroke–migraine depolarization continuum [4].

4. A Four-Phase Pathobiological Model of Migraine Aura

The pathogenesis of migraine aura can be organised into four neurobiological phases: pre-CSD vulnerability, initiation, glial propagation, and neuro-inflammatory transduction [4,15]. This framework, summarised in Figure 1 and Table 1, structures both the disease mechanism and the pharmacological intervention map.

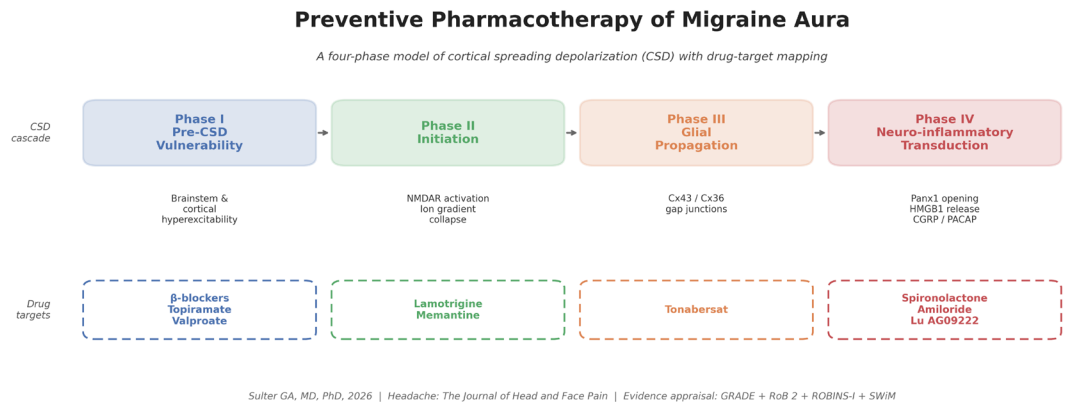

Figure 1. Four-phase pathobiological model of migraine aura with pharmacological intervention points. The four phases of CSD pathogenesis are depicted from left to right: Phase I (pre-CSD vulnerability), Phase II (initiation), Phase III (glial propagation), and Phase IV (neuro-inflammatory transduction). Pharmacological agents are mapped to their respective target phases. Drug boxes with solid red borders indicate agents with clinical trial evidence; dashed orange borders indicate preclinical/mechanistic evidence only; dashed blue borders indicate standard prophylactics.

Table 1. Four-phase pathobiological model of migraine aura with corresponding molecular targets and clinical expression.

Phase	Pathobiological features	Molecular targets	Pharmacological agents	Evidence level

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Phase I: Pre-CSD vulnerability	Brainstem modulation deficits; cortical hyperexcitability; deficient habituation	PAG, LC, DRN pathways; CACNA1A, ATP1A2, SCN1A	Standard prophylactics (β-blockers, valproate, topiramate)	High (non-aura population)
Phase II: Initiation	Ion homeostasis disruption; CaV-dependent Ca^{2+} buildup; threshold NMDAR activation	Voltage-gated Na^{+}/Ca^{2+} channels; NMDARs; K^{+} homeostasis	Lamotrigine; Memantine	Moderate; High (with caveats)*
Phase III: Glial propagation	Cx43/Cx36 gap-junction communication; intercellular Ca^{2+} waves; astrocytic syncytium	Connexin-43; Connexin-36 gap junctions	Tonabersat	Moderate (aura-specific Phase 2)†
Phase IV: Neuro-inflammatory transduction	Panx1 megachannel opening; caspase-1/HMGB1; NF-κB; trigeminovascular activation	Pannexin-1; ASICs; CGRP; PACAP-38	Spironolactone; Amiloride; Anti-PACAP (Lu AG09222)	Very Low; Low; High (non-aura)

Evidence levels (GRADE): High = RCT/meta-analysis data; Moderate = prospective observational; Low = retrospective/pilot; Very Low = preclinical only. *Memantine NMA based on general migraine populations; no aura-specific RCT available. †Tonabersat Phase 2 positive for aura; general migraine trials negative. See text for critical appraisal.

Table 2. Summary of repurposed and pipeline medications for migraine aura prevention.

Agent	Mechanism	Phase targeted	Evidence level	Clinical status	Key limitation
Lamotrigine	Na^{+}/Ca^{2+} channel blockade; glutamate reduction	II (Initiation)	Moderate	Open-label positive	No aura-specific RCT
Memantine	Uncompetitive NMDAR antagonism	II (Initiation)	High (indirect, aura subgroup absent)	NMA favourable	No aura-subgroup data; NNT ≈ 4.9
Spironolactone	Pannexin-1 channel inhibition	IV (Transduction)	Very Low	Hypothesis only	~50× PK gap; MR antagonism dose-limiting
Amiloride	ASIC1a blockade	III–IV	Low	Pilot positive; APAM trial pending	n=7 case series only
Tonabersat	Cx36/Cx43 gap-junction inhibition	III (Propagation)	Moderate	Phase 2 positive (aura); Phase 3 not pursued	Patient selection failure; 16.6% attrition
Lu AG09222	Anti-PACAP-38 monoclonal antibody	IV (Transduction)	High	Phase 2 positive (HOPE)	Aura-specific data pending

NMA, network meta-analysis; RCT, randomised controlled trial; CI, confidence interval; OR, odds ratio; MR, mineralocorticoid receptor; Panx1, pannexin-1; ASIC, acid-sensing ion channel; PK, pharmacokinetic.

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4.1. Phase I — Pre-CSD Vulnerability and Triggers

Before CSD can be ignited, the cortex must reside in a heightened-excitability state. Functional and structural abnormalities in the periaqueductal grey, locus coeruleus, and dorsal raphe nucleus reduce descending inhibitory control [1,16], and patients with migraine with aura exhibit deficient habituation of visually evoked cortical responses [3]. Genetic predisposition amplifies vulnerability: gain-of-function CACNA1A (CaV2.1, FHM1), loss-of-function ATP1A2 (Na^+/K^+-ATPase, FHM2), and gain-of-function SCN1A (NaV1.1, FHM3) chronically lower the CSD threshold [17,18].

Three trigger classes are mechanistically informative. (i) High-contrast striped stimuli and flickering light specifically provoke visual aura through deficient occipital habituation and sustained excitatory neurotransmitter release [3,19]. (ii) Microembolic signals are more frequently detectable during complex aura, and focal hypoxia activates stress-sensitive astrocytic and neuronal channels that lower the CSD threshold [2,10]. (iii) Intravenous levcromakalim, a synthetic KATP channel opener, provokes migraine in 100% of migraine patients—the most potent pharmacological trigger identified to date—through massive K^+ efflux causing hyperpolarization and rebound depolarization toward the CSD initiation threshold.

4.2. Phase II — Initiation: Ion Homeostasis and NMDA Receptor Dynamics

CSD initiation requires disruption of ion homeostasis surpassing a defined depolarization threshold. Initiation requires delayed, threshold-dependent activation of NMDARs mediated by a preceding CaV-dependent buildup of intracellular calcium [19]. Pharmacological blockade of NMDARs or CaV channels completely inhibits CSD initiation, establishing both as critical therapeutic targets [7]. Vitale et al. (2025), using FHM1 knock-in mice, showed that the NMDAR activation threshold for CSD initiation is identical to wild-type but is reached at lower stimulus intensity in FHM1, identifying CaV2.1–NMDAR crosstalk as the critical determinant of CSD susceptibility [20].

4.3. Phase III — Propagation via the Astrocytic Syncytium

Following initiation, CSD propagates through the astrocytic syncytium interconnected via connexin-43 (Cx43) and connexin-36 (Cx36) gap junctions, with intercellular calcium waves sustaining propagation [21]. Optogenetic models confirm CSD originating from primary visual cortex propagates via these glial networks and induces migraine-like pain behaviour in freely moving animals [8]. Pharmacological or genetic gap-junction inhibition significantly attenuates CSD expansion [21,22].

4.4. Phase IV — Neuro-inflammatory Transduction

The bridge between painless cortical depolarization and headache is formed by activation of pannexin-1 (Panx1) megachannels [15]. Panx1 opening triggers caspase-1 activation and release of pro-inflammatory DAMPs—particularly HMGB1—activating NF-κB signalling in astrocytes, propagating to the glia limitans and meninges, and activating the trigeminovascular system [1,13,15]. The Moskowitz (2025) buildup hypothesis adds that noxious mediators may need to accumulate to a critical concentration before trigeminal activation occurs, explaining the variable temporal relationship between aura onset and headache [5].

5. Current Preventive Practice and Its Limitations

Standard preventive medications—beta-blockers, antiepileptics, tricyclic antidepressants—chronically elevate the CSD initiation threshold and suppress CSD frequency by 40–80% in experimental models [7], but require prolonged treatment, provide partial efficacy, and carry substantial adverse effects [1,7]. CGRP-targeted biologicals fail to reach the cortical parenchyma to inhibit CSD [1,4]; clinically meaningful aura attacks therefore persist despite adequate headache control [4,5]. Recent evidence confirms that CGRP does not directly alter CSD ionic mechanisms but

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modulates pain pathways downstream of cortical depolarization [23], reinforcing the need for mechanistically distinct aura-specific agents.

6. Rationale-Driven Drug Repurposing for Aura Prevention

Repurposing existing medications targeting specific CSD cascade components offers an immediately available strategy. Below, agents with clinical trial data (Section 6.1) are distinguished from those supported exclusively by preclinical/mechanistic evidence (Section 6.2).

6.1. Agents with Clinical Evidence

6.1.1. Lamotrigine (Initiation, Moderate Evidence)

Lamotrigine, a state-dependent blocker of voltage-gated sodium and calcium channels, reduces pathological presynaptic glutamate release and directly interferes with Phase II initiation [24]. A 2025 observational study of 37 patients exclusively with migraine with aura reported a ≥50% aura reduction in 97.3% at six months (50–100 mg/day), with mean attack frequency falling from 4 to 1 per month. Earlier retrospective evidence suggested comparable efficacy to topiramate with better tolerability [24].

Critical appraisal: Reported high responder rates derive from unblinded, uncontrolled, single-centre observational studies susceptible to selection bias, performance bias, and regression to the mean [24]. Earlier open-label studies reported reductions in aura frequency while headache frequency was less affected—pharmacologically consistent with a CSD-specific mechanism, but possibly reflecting the natural variability of the aura endpoint. Confirmation requires a placebo-controlled RCT with aura-specific primary endpoints before lamotrigine can be recommended as evidence-based aura prophylaxis.

6.1.2. Memantine (Initiation, High Evidence with Caveats)

Because NMDAR activation is required for CSD initiation, the uncompetitive antagonist memantine is a rational prophylactic. Its low-affinity, voltage-dependent blockade selectively attenuates pathological NMDAR activation while preserving physiological synaptic transmission [25,26]. A 2024 systematic review and network meta-analysis of 38 RCTs (>13,000 participants) ranked memantine highest for 50% responder rate (OR 5.58; 95% CI 2.41–12.92) and one of the largest reductions in monthly migraine days, with the lowest dropout rate among compared prophylactics [25]. In individual RCTs, memantine 10–20 mg/day reduced migraine frequency from ~10.8 to 2.6 days/month at 24 weeks [26]. A comprehensive review of NMDAR antagonists in migraine has confirmed that both memantine and ketamine inhibit spreading depolarization propagation [27].

Critical appraisal: The 95% CI (2.41–12.92) is wide, the network is powered by only three single-centre memantine RCTs (India, Mexico, Iran), and—most critically—the contributing trials enrolled general migraine populations without aura stratification; the authors explicitly acknowledged the inability to construct aura-specific subnetworks [25]. SUCRA point estimates rely heavily on indirect evidence and may be optimistic. Direct extrapolation to aura prevention is therefore unjustified.

Quantifying the evidence gap: Using the conservative lower CI bound (OR 2.5), placebo 50% responder rate of 25%, two-sided α=0.05, and 80% power, a two-group proportion comparison yields 85 patients per arm (170 evaluable), NNT≈4.9. Because realistic dropout reduces the analysable population, the enrolled sample must be inflated by 1/(1−d): with d=0.20 this requires 170/0.80 ≈ 214 enrolled (107/arm); for 90% power, 226 evaluable / 284 enrolled (142/arm). A definitive aura-specific memantine RCT is feasible within the recruitment capacity of a multicentre European headache network. The field's failure to conduct such a trial represents a correctable methodological gap—not a fundamental barrier to progress.

6.2. Agents with Preclinical or Mechanistic Evidence Only

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Spironolactone (Very Low evidence) was identified as a potent inhibitor of pannexin-1 channels [28], the molecular switch linking CSD to neuro-inflammatory transduction [15]. Translational barriers are formidable: in vitro Panx1-inhibiting concentrations (~10 μM) substantially exceed the peak plasma concentrations achievable with standard doses (50–100 mg; Cmax ~80 ng/mL ≈ 0.2 μM)—a ~50-fold gap [28]. Even if achievable, dose-limiting potassium retention and haemodynamic effects from primary mineralocorticoid receptor antagonism would preclude suprapharmacological dosing. Spironolactone therefore remains a pharmacological proof of principle for Panx1 as a target rather than a viable clinical candidate.

Amiloride (Low evidence) targets acid-sensing ion channels (ASICs), particularly ASIC1a, activated by tissue acidification during CSD [29]. A single open-label case series (n=7) reported reduced aura frequency in four patients over 6–24 months [29]; the APAM proof-of-concept trial (NCT04063540) is awaited.

7. The Emerging Pharmacological Pipeline (2025–2030)

7.1. Gap-Junction Modulators: Tonabersat

Tonabersat is a benzopyran selectively inhibiting Cx36/Cx43 gap-junction communication, directly targeting Phase III propagation [21,22]. In a pivotal Phase 2 randomised, double-blind, placebo-controlled crossover trial (n=47), tonabersat 40 mg/day reduced median aura attacks from 3.2 to 1.0 per 12-week period (p=0.01), with no significant efficacy for non-aura migraine attacks [22]—an aura-specific profile distinguishing tonabersat from all currently available prophylactics.

Analysis of subsequent failures: Tonabersat did not progress to Phase 3 for migraine. Two subsequent randomised trials (total n=199) for general migraine prevention and acute treatment yielded negative results [30]. Critical analysis identifies four contributing factors: (i) failure to enrich for aura, diluting the target population [30]; (ii) pharmacokinetic unsuitability for acute treatment (Tmax 2–3 h in healthy volunteers, longer during attacks due to gastric stasis) [30]; (iii) small sample sizes; and (iv) substantial attrition bias—33 patients (16.6%) lost to follow-up without identified cause in one trial, exceeding the CONSORT 5% threshold by a factor of 3.3 [30].

Worst-case ITT sensitivity analysis: Under the conceptual worst case in which all unaccounted dropouts are assigned baseline aura frequency, a hypothetical aura-enriched replication trial (n=100, 16.6% attrition) would produce an ITT mean aura frequency of 1.37 versus 3.2 placebo—a 57.1% reduction, statistically significant (Cohen's d=0.91, p<0.001) and clinically meaningful. The aura-specific signal observed by Hauge et al. [22] is robust to attrition bias. Failure of tonabersat in general migraine reflects inappropriate patient selection, pharmacokinetic unsuitability for acute use, and underpowered designs—not invalidation of the gap-junction modulation hypothesis.

Post-hoc minimum-detectable-effect analysis: With a monthly aura baseline of 3.2 (SD ≈2.2) per Hauge et al., the pooled Phase 3 evaluable aura sample of ~100/arm yielded 80% power to detect Cohen's d ≥0.40 (α=0.05, two-sided)—≈0.87 absolute aura attacks/month, or ~27% relative reduction. Phase 2 had observed an effect ~3× larger (d≈1.0, 69% reduction), for which n=100/arm would deliver >99% power. Phase 3 was therefore not statistically underpowered; failure signals either Phase 2 effect inflation by aura enrichment or dilution of a genuine aura-specific gap-junction effect in broader chronic/episodic populations. Both are falsifiable hypotheses; an enriched-design RCT (≥3 aura/month, confirmed phenotype) would provide a decisive retest.

7.2. Tissue-Selective KATP Channel Antagonists

Given that KATP openers reliably trigger migraine and aura, selective KATP antagonists are a logical target. Cranial-vascular KATP channels predominantly comprise Kir6.1/SUR2B, distinct from pancreatic Kir6.2/SUR1. Before first-in-human trials, any KATP antagonist candidate should demonstrate an IC50 selectivity ratio >100-fold for vascular Kir6.1/SUR2B over pancreatic Kir6.2/SUR1, to avoid dysglycaemia and cardiovascular liabilities that curtailed earlier non-selective agents (e.g., glibenclamide cross-reactivity).

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7.3. Anti-PACAP-38 Monoclonal Antibodies

PACAP-38 has emerged as a pivotal migraine mediator operating through PAC1, VPAC1, and VPAC2 receptors [31]. Lu AG09222, a humanised anti-PACAP antibody, significantly reduced monthly migraine days versus placebo (−6.2 vs −4.2; difference −2.0 days; p=0.02) over 4 weeks in the Phase 2 HOPE trial (n=237) [31]. The Phase 2 PROCEED dose-finding trial (n=498) is anticipated to complete in 2025. Whether anti-PACAP antibodies specifically address CSD and aura, in addition to headache, requires prospective investigation in aura-enriched populations.

8. Measuring What Cannot Be Seen: Silent CSD in Clinical Trials

If CSD propagation that does not produce overt aura nonetheless contributes to headache generation [5], then conventional endpoints (aura attack frequency, aura duration, headache days) may be insufficiently sensitive to detect the full benefit of CSD-suppressing agents. This concern is not theoretical: tonabersat's Phase 2 aura-specific efficacy but Phase 3 failure may partly reflect inability of standard endpoints to capture suppression of silent CSD events.

Emerging modalities offer potential surrogate biomarkers. Noninvasive high-resolution direct-current electroencephalography (DC-EEG) has demonstrated proof-of-concept CSD detection; neuron-derived extracellular vesicles (EVs) have been proposed as circulating biomarkers; magnetoencephalography (MEG) has evolved to 306-channel systems with potential for noninvasive spreading depolarization detection [9]. Translational deployment of surface DC-EEG requires two validation steps not yet adequately completed: (i) concurrent recording against invasive electrocorticography to establish sensitivity/specificity; and (ii) artifact rejection protocols separating true sub-millivolt scalp DC shifts (typically 200–500 μV after volume-conduction attenuation, propagation 2–5 mm/min, time-locked to aura) from motion, ocular, and galvanic artifacts of comparable amplitude.

A hypothesis explaining all possible outcomes risks becoming unfalsifiable. The silent CSD hypothesis must be constrained by pre-specified falsification criteria. We propose the following thresholds. DC-EEG: a trial is negative for CSD suppression if <20% of treatment-arm patients demonstrate ≥50% reduction in DC-EEG slow potential shift events (scalp amplitude in the order of 200–500 μV, duration 30–90 s, propagation 2–5 mm/min, time-locked to a documented aura event), versus baseline. The historical electrocorticographic shift range of 5–20 mV cannot be transposed directly to the scalp; a ≥5 mV scalp excursion should be treated as artefact unless concurrent ECoG or 306-channel MEG corroboration is available. Circulating EVs: a null result is declared if the treatment arm fails a statistically significant reduction (α=0.05, power ≥80%) in multi-marker neuron-derived EV concentration—particles/mL co-positive for L1CAM (CD171) AND SNAP25 (or synaptophysin/neurogranin)—at 12 weeks versus placebo, with the minimal clinically important difference pre-specified as ≥30% reduction from baseline. Reliance on L1CAM alone is now considered insufficient because L1CAM is also detectable on soluble proteins and non-neuronal vesicles. These thresholds transform the silent CSD hypothesis from an unfalsifiable explanatory framework into a testable set of predictions.

9. Conclusion: A Seven-Point Methodological Framework for Future Trials

The four-phase pathobiological model presented here provides a structured framework for identifying and evaluating aura-specific therapeutic interventions. Yet this critical appraisal reveals a sobering conclusion: despite compelling mechanistic rationale, no candidate agent currently possesses Level A evidence from an aura-specific, adequately powered RCT. Memantine and lamotrigine target Phase II initiation but require validation in dedicated aura populations [25]; spironolactone faces a ~50-fold pharmacokinetic concentration gap for Panx1 inhibition [28]; amiloride awaits APAM controlled data [29]. Among pipeline agents, tonabersat has provided the most rigorous aura-specific proof of concept, and our worst-case ITT sensitivity analysis confirms its development stalled due to trial design—not biological signal [22,30].

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To guide the next generation of aura-prevention trials and ensure falsifiability, we propose seven testable methodological predictions:

H1 — Memantine aura-specific RCT: A multicentre, double-blind, placebo-controlled RCT of memantine 10–20 mg/day enrolling 214 patients with migraine with aura (107/arm; 170 evaluable after 20% attrition, calculated as n/(1−d)), powered at 80% to detect a conservative OR of 2.5 for the 50% aura responder rate (NNT≈4.9), will demonstrate a statistically significant reduction in aura attack frequency at 24 weeks. If negative, NMDAR-targeted CSD initiation blockade should be reclassified from Level A (with caveats) to Level B for aura prevention.

H2 — Lamotrigine confirmation: A sham-controlled RCT of lamotrigine 50–100 mg/day in migraine with aura will replicate the ≥50% aura responder rate observed in observational studies, with aura frequency as the pre-specified primary endpoint.

H3 — Tonabersat re-evaluation: Re-evaluation of tonabersat 40 mg/day or a next-generation gap-junction modulator in an aura-enriched population (ICHD-3 migraine with aura, ≥2 aura/month at baseline) using a prophylactic dosing regimen and aura attack frequency as the primary endpoint will reproduce the Hauge et al. effect size (≥68% aura reduction) in a parallel-group design.

H4 — Non-invasive CSD detection: Ambulatory high-resolution scalp DC-EEG—or, alternatively, a 306-channel magnetoencephalography (MEG) array [9]—will detect CSD-associated slow potential or low-frequency magnetic shifts (scalp DC amplitude in the order of 200–500 μV after volume-conduction attenuation through skull and scalp; propagation velocity 2–5 mm/min) co-registered against a positive aura diary in ≥40% of monitored aura events within a 12-week observation period. Direct cortical (electrocorticographic) shifts of 5–20 mV cannot be assumed to translate to scalp without massive amplitude attenuation; any apparent ≥5 mV scalp DC excursion should be presumed artefactual (galvanic skin response, ocular drift) until proven otherwise. If the μV-scale, multimodal threshold is not met across two independent cohorts, non-invasive CSD biomarkers should be considered insufficient as a primary surrogate endpoint.

H5 — Extracellular vesicle biomarker: Multi-marker neuron-derived EV concentrations in peripheral blood—co-positive for L1CAM (CD171) AND a transmembrane synaptic marker such as SNAP25 (or alternatively synaptophysin/neurogranin), to overcome the recognised non-exclusivity of L1CAM and its presence on soluble proteins—will show ≥30% reduction from baseline in patients achieving ≥50% aura reduction with any CSD-targeting agent. Failure across two independent trials with the multi-marker definition should retire the biomarker as a CSD surrogate.

H6 — Anti-PACAP aura subgroup: Pre-specified aura subgroup analysis of the PROCEED trial (Lu AG09222) will reveal a differential treatment effect, with greater migraine day reduction in patients with ≥2 aura/month versus those without aura.

H7 — Silent CSD and headache dissociation: In trials employing both DC-EEG monitoring and headache diaries, a subgroup will demonstrate objective CSD suppression (≥50% DC-EEG event reduction) without proportional headache reduction—providing the first direct evidence that silent CSD contributes to headache generation through the Moskowitz buildup mechanism, or refuting the hypothesis if CSD suppression and headache reduction are tightly correlated.

By integrating CSD pathobiology with rigorous, quantitative, and falsifiable predictions, the burden of migraine aura can be addressed with unprecedented precision—provided the field commits to the methodological rigour that this complex neurobiological target demands.

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