

# Therapeutic Transition Protocols for Geriatric Post-Acute Sequelae: A Chronopharmacological Approach to Natural Substitution

## Introduction

The clinical management of post-acute sequelae in the geriatric population necessitates a paradigmatic shift away from the blunt instruments of synthetic polypharmacy toward a nuanced, restorative approach utilizing naturally effective substances. The aging physiological milieu, characterized by immunosenescence, endothelial rigidity, and a reduced threshold for homeostatic disruption, is ill-suited for the aggressive side-effect profiles of high-risk synthetic medications. Seniors often find themselves caught in a cascade of prescriptions where one agent is introduced to mitigate the adverse effects of another, leading to a pharmacological burden that impedes genuine recovery.

The objective of this report is to provide a rigorous, evidence-based protocol for substituting high-risk synthetic agents with natural compounds that possess demonstrated efficacy in modulating the underlying pathologies of inflammation, mitochondrial dysfunction, and vascular compromise. This approach moves beyond symptom suppression to target the molecular roots of dysfunction—specifically the "cytokine storm" remnants, mast cell activation, and oxidative stress—using a sophisticated overlapping schedule of therapeutic sets.

## Chapter 1: The Overlapping Chronopharmacological Schedule

Therapeutic efficacy in natural medicine, particularly for the elderly, relies heavily on the temporal orchestration of dosing. The "one-pill-once-a-day" model often fails to respect the pharmacokinetics of natural substances or the circadian rhythms of the body's repair processes. The following protocol is structured around **six distinct sets** of therapeutic agents, arranged in an overlapping monthly and bi-monthly schedule. This design ensures continuous coverage for critical systems (vascular, mitochondrial) while employing cyclical dosing for immunomodulators to prevent tolerance (tachyphylaxis) and pulse dosing to reset sensory thresholds.

### The Chronopharmacological Rationale

The schedule is constructed on three temporal planes to maximize efficacy and minimize pill

burden:

1. **Continuous Foundation:** Daily administration of agents required for structural and metabolic integrity (endothelial NO production, ATP synthesis).
2. **Cyclical Modulation:** Long-duration cycles (60-90 days) for agents targeting neuroplasticity and immune modulation, allowing for tissue regeneration windows.
3. **Pulse Interventions:** Short-duration, high-intensity pulses (14 days) to stimulate sensory pathways without inducing habituation.

## The Master Schedule Matrix: Overlapping Sets

The following matrix outlines the administration of Sets 1 through 6, detailing the overlap of continuous, cyclical, and pulsed dosing regimens.

Therapeutic Set	Components	Dosing Rhythm	Temporal Logic & Circadian Alignment
<b>Set 1: Metabolic Core</b>	L-Arginine + Liposomal Vitamin C  Coenzyme Q10 (Ubiquinol)	<b>Continuous / Daily</b>  <i>Morning &amp; Early Afternoon</i>	<b>Nitric Oxide Half-Life Extension:</b> L-Arginine is dosed twice daily to maintain steady-state NO levels, countering the rapid degradation typical in aged endothelium. Vitamin C prevents eNOS uncoupling. Ubiquinol is dosed early to align with diurnal mitochondrial demand and avoid evening stimulation. <sup>1</sup>
<b>Set 2: Neurovascular</b>	Ginkgo Biloba Extract (EGb 761)	<b>Continuous / Daily</b>	<b>Cognitive Demand Matching:</b> Dosed

		<i>Morning &amp; Mid-day</i>	to peak during hours of highest executive function requirement. The continuous anti-platelet factor activity replaces synthetic blood thinners safely. <sup>1</sup>
<b>Set 3: Immuno-Restoration</b>	<b>Echinacea, Propolis, &amp; Rosehip Formulation</b>	<b>Bi-Monthly Cycle</b> <i>2 Months ON / 1 Month OFF</i>	<b>Prevention of Tolerance:</b> Continuous immunostimulation can lead to receptor downregulation or immune exhaustion. A 2-month "ON" phase reduces inflammatory markers (CRP), while the 1-month "OFF" phase allows system reset. <sup>1</sup>
<b>Set 4: Neuro-Repair</b>	<b>Micronized PEA + Luteolin (Co-ultraPEALut)</b>	<b>Quarterly Cycle</b> <i>3 Months ON (90 Days)</i>	<b>Regenerative Window:</b> The 90-day duration corresponds to the regenerative cycle of olfactory neurons and the stabilization of glial cells. Shorter cycles are insufficient for neurostructural repair; longer cycles are generally unnecessary once

			homeostasis is restored. <sup>1</sup>
<b>Set 5: Sensory Pulse</b>	<b>Aromatherapy Blend</b> <i>(Thyme, Orange, Clove, Frankincense)</i>	<b>Pulse Dosing</b> <i>14 Days ON / 14 Days OFF</i>	<b>Sensory Resensitization:</b> Olfactory receptors habituate rapidly (olfactory fatigue). A 14-day pulse provides intense limbic stimulation to combat fatigue, followed by a 14-day washout to maintain receptor sensitivity. <sup>1</sup>
<b>Set 6: Circadian Anchor</b>	<b>Melatonin</b>	<b>Continuous / Nightly</b> <i>30 mins before sleep</i>	<b>Glymphatic Clearance:</b> Administered specifically to coincide with the opening of the lymphatic system during sleep, facilitating the clearance of neurotoxins accumulated during the day. Acts as a potent CNS antioxidant. <sup>1</sup>

## Detailed Execution of the Sets

### Set 1: The Vascular and Mitochondrial Engine (Morning & Early Afternoon)

This set addresses the primary energetic and perfusory deficits in seniors. The combination of L-Arginine (1.66 g) and Liposomal Vitamin C (500 mg) is critical. In the elderly, the enzyme endothelial nitric oxide synthase (eNOS) often becomes "uncoupled," producing superoxide radicals instead of nitric oxide, which damages vessels further. Vitamin C is essential to recouple this enzyme. Coenzyme Q10 in the form of Ubiquinol (100 mg) is added to drive the electron transport chain, directly combating the mitochondrial exhaustion that defines post-acute fatigue.

- *Dosing Schedule:* Taken twice daily. It is imperative that this set is maintained continuously without breaks, as the half-life of these nutrients is short and endothelial dysfunction returns rapidly upon cessation.<sup>1</sup>

#### Set 2: Cognitive Perfusion (Morning)

Set 2 consists of Ginkgo Biloba Extract (EGb 761), dosed at 80 mg twice daily. This serves as the "cognitive bridge," ensuring adequate microcirculation to the cerebral cortex. The extract's terpene lactones reduce blood viscosity, effectively acting as a milder, safer alternative to synthetic anticoagulants for maintaining cerebral perfusion.

- *Dosing Schedule:* Continuous daily use. Morning and mid-day dosing prevents evening alertness that might interfere with sleep architecture.<sup>1</sup>

#### Set 3: The Immune Modulator (Bi-Monthly)

This set targets the chronic low-grade inflammation ("inflammaging") prevalent in seniors. The formulation of Echinacea, Propolis, and Rosehip is not used as an acute antimicrobial here, but as a modulator of cytokine expression.

- *Dosing Schedule: Two Months ON / One Month OFF.* The rationale for this cyclical approach is rooted in the dynamics of the immune system; prolonged, uninterrupted stimulation of alveolar macrophages and natural killer cells can lead to diminishing returns. The "break" month ensures that the immune system remains responsive to the modulation.<sup>1</sup>

#### Set 4: The Neuro-Inflammation Quencher (Quarterly)

This set is the cornerstone for treating sensory loss and "brain fog." It utilizes Micronized Palmitoylethanolamide (PEA) and Luteolin.

- *Dosing Schedule: 3 Consecutive Months (90 Days).* The 90-day period is empirically derived from clinical trials on olfactory dysfunction, where significant recovery curves were observed peaking at the 3-month mark. Premature cessation (e.g., at 30 days) often results in incomplete recovery of the neuro-epithelium.<sup>1</sup>

#### Set 5: The Energy Pulse (Monthly Intermittent)

To address subjective fatigue and lethargy without using adrenergic stimulants (which risk cardiovascular events in seniors), this set employs olfactory stimulation.

- *Dosing Schedule: 14 Days ON / 14 Days OFF.* Patients inhale the essential oil blend twice daily for two weeks. This "pulse" stimulates the limbic system and hypothalamus to modulate perceived energy levels. The 14-day "OFF" period is mandatory to prevent olfactory adaptation, ensuring the therapy remains effective month after month.<sup>1</sup>

#### Set 6: The Circadian Reset (Nightly)

Melatonin is dosed nightly to address the calcification of the pineal gland common in aging.

- *Dosing Schedule:* Continuous nightly use. This is not cycled, as the age-related decline in endogenous melatonin is permanent and requires constant supplementation to maintain sleep architecture and nocturnal antioxidant protection.<sup>1</sup>

# Chapter 2: Considering Replacement with Western Medicine

The transition from synthetic to natural pharmacotherapy in the elderly requires a sophisticated understanding of drug mechanisms. The goal is to replace the *function* of the drug without incurring its *toxicity*. This is particularly challenging in seniors who are often prescribed "cocktails" of medications—typically combinations of drug classes such as antihypertensives, statins, anticoagulants, and antidepressants.

## The Replacement Matrix for Complex Drug Profiles

The following analysis presents a substitution matrix for elderly patients, specifically addressing those prescribed a **combination of two drug classes**. It details the natural agents that fit into these pharmacological profiles, their mechanisms of substitution, and the critical circadian timing for administration.

### Profile A: The "Cardio-Metabolic" Patient

**Current Regimen:** Anticoagulants / Anti-platelets (e.g., Aspirin, Clopidogrel) + Antidiabetic Agents (e.g., Metformin, Sulfonylureas).

Synthetic Drug Class	Natural Substitute	Mechanism of Substitution	Circadian Timing
Anticoagulants	Salmon Oil + Resveratrol	<b>Endothelial Resolution:</b> Rather than irreversibly poisoning platelet cyclooxygenase (like Aspirin), Salmon Oil (Omega-3s) and Resveratrol improve endothelial non-adhesiveness and reduce blood viscosity. This reduces thrombotic risk without the high risk of gastric hemorrhage.	<b>Morning (with Food):</b> Absorption of lipid-soluble Omega-3s is maximal with dietary fat. Morning dosing aligns with the circadian peak of platelet aggregation. <sup>1</sup>

		associated with daily aspirin use in seniors. <sup>1</sup>	
<b>Antidiabetics</b>	<b>Ficus pumila Extract + Nigella sativa</b>	<b>Sensitization &amp; Secretion:</b> <i>Ficus pumila</i> stimulates insulin secretion in a glucose-dependent manner, reducing hypoglycemia risk. <i>Nigella sativa</i> improves insulin sensitivity (AMPK activation) and lipid profiles, mimicking the dual benefits of Metformin and Statins. <sup>1</sup>	<b>Before Meals:</b> Administered 15-30 minutes pre-prandial to blunt the glucose spike, mimicking the physiological insulin response. <sup>1</sup>

**Synthesis:** For the patient on Profile A, the combination of Salmon Oil/Resveratrol in the morning and Ficus/Nigella before meals provides a "vascular safety net" that addresses both the viscosity of the blood and the metabolic dysregulation that damages the vessel walls, replacing the blunt trauma of synthetic blood thinners and hypoglycemics.

### Profile B: The "Neuro-Affective" Patient

**Current Regimen:** Antidepressants / Anxiolytics (e.g., SSRIs, Benzodiazepines) + Cognitive Enhancers (e.g., Donepezil, Memantine).

Synthetic Drug Class	Natural Substitute	Mechanism of Substitution	Circadian Timing
Anxiolytics	Lavender Oil (Silexan)	<b>Voltage-Gated Modulation:</b> Silexan modulates calcium channels in neurons (similar to pregabalin mechanism) to reduce excitability	<b>Anytime (Non-sedating):</b> Can be taken with breakfast or lunch. Unlike benzos, it does not induce daytime somnolence,

		without the GABA-ergic sedation of benzodiazepines. It allows for anxiety relief without increasing fall risk—a critical factor in geriatrics. <sup>1</sup>	allowing the senior to remain active. <sup>1</sup>
<b>Cognitive Enhancers</b>	<b>Ginkgo Biloba (EGb 761)</b>	<b>Mitochondrial Protection:</b> Instead of merely inhibiting acetylcholinesterase (which causes nausea Bradycardia), EGb 761 enhances cerebral blood flow and protects neuronal mitochondria from amyloid toxicity, preserving cognitive function via structural support. <sup>1</sup>	<b>Morning &amp; Mid-day:</b> Dosing aligns with cognitive demand. Avoids evening dosing to prevent vivid dreams sometimes associated with cerebral activation. <sup>1</sup>

**Synthesis:** Profile B patients often suffer from the "prescribing cascade" where donepezil causes agitation, leading to a prescription for benzodiazepines. Switching to Ginkgo and Silexan breaks this cycle. Ginkgo improves perfusion to support cognition, while Silexan manages anxiety without sedation, preserving the patient's autonomy and balance.

### Profile C: The "Inflammatory-Fibrotic" Patient

**Current Regimen:** Corticosteroids (e.g., Prednisone) + Antifibrotics (e.g., Nintedanib).

Synthetic Drug Class	Natural Substitute	Mechanism of Substitution	Circadian Timing
Corticosteroids	PEA + Luteolin	<b>ALIA Mechanism:</b> PEA acts as an endogenous	<b>Morning &amp; Evening (BID):</b> Consistent blood

		PPAR- $\alpha$ agonist, stabilizing mast cells and downregulating pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ ) akin to steroids but without immune suppression or adrenal suppression. <sup>1</sup>	levels are required to mimic the steady-state anti-inflammatory effect of long-acting steroids. <sup>1</sup>
<b>Antifibrotics</b>	<b>Tocotrienol-Rich Fraction (TRF) + Carotene</b>	<b>Cytokine Downregulation:</b> TRF and Carotene downregulate TGF- $\beta$ /Smad signaling pathways, the master regulators of fibrosis. This offers tissue protection without the severe liver toxicity and gastrointestinal distress common with synthetic antifibrotics. <sup>1</sup>	<b>Morning:</b> Antioxidant protection is best established early to counter oxidative stress generated during the day's metabolic activity. <sup>1</sup>

**Synthesis:** Profile C represents patients with severe post-acute lung sequelae or autoimmune conditions. The combination of PEA/Luteolin and TRF provides a potent anti-inflammatory and anti-fibrotic shield that mimics the *intent* of steroids and antifibrotics but utilizes physiological signaling pathways (PPAR- $\alpha$ , TGF- $\beta$  modulation) rather than gross immune suppression.

## Chapter 3: Efficacy-Based Analysis of Therapeutic Agents

This section provides an exhaustive analysis of the therapeutic agents employed in this protocol, sorted by their efficacy and the strength of the supporting scholarly evidence. For each agent, we detail the mechanism of action, specific clinical results from relevant studies,

and the optimal dosing strategy.

## 1. Palmitoylethanolamide (PEA) and Luteolin (Co-ultraPEALut)

**Efficacy Rank:** Highest (Primary Disease-Modifying Intervention)

Mechanism of Action: The ALIA Phenomenon

Palmitoylethanolamide (PEA) is an endogenous fatty acid amide, a lipid mediator produced "on demand" by cells in response to stress. Its primary mechanism is the activation of the nuclear receptor PPAR- $\alpha$  (Peroxisome Proliferator-Activated Receptor alpha). Unlike synthetic anti-inflammatories that block enzymes (COX-1/2), PEA binds to PPAR- $\alpha$ , which then translocates to the nucleus to downregulate the transcription of pro-inflammatory genes (e.g., TNF- $\alpha$ , IL-1 $\beta$ , iNOS).<sup>4</sup>

Crucially, PEA operates via the **ALIA mechanism (Autacoid Local Injury Antagonism)**, first described by Nobel Laureate Rita Levi-Montalcini. This mechanism involves the stabilization of non-neuronal cells, specifically **mast cells** and **microglia**.<sup>5</sup> By preventing mast cell degranulation, PEA halts the release of the "cytokine storm" mediators at the source. Furthermore, PEA exhibits an "entourage effect," inhibiting the degradation of the endocannabinoid anandamide, thereby indirectly activating cannabinoid receptors (CB1, CB2) and TRPV1 channels to modulate pain and neuroinflammation.<sup>3</sup> Luteolin, when co-ultramicronized with PEA, acts as a potent antioxidant, preventing the oxidative degradation of PEA and enhancing its neuroprotective reach.<sup>7</sup>

Scholarly Studies & Clinical Results

The clinical pedigree of PEA is extensive and robust, yet often overlooked due to geopolitical factors in the 20th century.

- **Historical Efficacy (The "Impulsin" Trials):** In the 1970s, PEA (branded as *Impulsin*) was evaluated in Czechoslovakia in six double-blind, placebo-controlled trials involving nearly 4,000 subjects. These trials focused on influenza and respiratory tract infections. The results were statistically significant: prophylactic use of PEA reduced the incidence of acute respiratory disease (ARD) and markedly reduced symptom severity (fever, headache, sore throat).<sup>8</sup> For instance, in a 1973 trial, ARD incidence was **22.7%** in the PEA group versus **34.4%** in the placebo group.<sup>9</sup>
- **Olfactory Recovery (Smell):** In the context of post-acute sensory loss, a multicenter, double-blinded, randomized placebo-controlled trial involving 185 patients demonstrated that the combination of PEA and Luteolin (Co-ultraPEALut) significantly improved olfactory threshold and identification scores. Another study indicated that **92%** of patients in the PEA-Luteolin intervention group showed improvement versus only **42%** of controls. Specifically, for parosmia (distorted smell), the combination of PEA + Luteolin + Alpha-Lipoic Acid achieved a **96%** resolution rate after 6 months.<sup>2</sup>
- **Visual & Auditory Protection:** PEA has been shown to lower intraocular pressure (IOP) in glaucoma patients and suppress Müller gliosis in diabetic retinopathy models.<sup>11</sup> In auditory models, PEA modulation of neuroinflammation prevents noise-induced synaptic

imbalance, suggesting efficacy for tinnitus, which is fundamentally a neuroinflammatory condition of the auditory cortex.<sup>13</sup>

#### **Dosage & Schedule:**

- **Dosage:** 700 mg PEA + 70 mg Luteolin (ultramicronized).
- **Schedule:** Daily administration, **twice a day**, for a strict **90-day cycle**.
- **Rationale:** The 90-day duration is critical; clinical data indicates that recovery curves for olfactory and neurocognitive function plateau at the 3-month mark. Daily dosing is superior to intermittent dosing for this agent because it requires sustained plasma levels to keep PPAR- $\alpha$  receptors activated and mast cells stabilized.<sup>1</sup>

## **2. L-Arginine + Liposomal Vitamin C**

**Efficacy Rank:** High (Vascular & Fatigue Restoration)

Mechanism of Action: Recoupling eNOS

This combination addresses the "uncoupled" endothelial state in seniors. L-Arginine is the substrate for Nitric Oxide (NO), but without adequate antioxidant cofactors, endothelial nitric oxide synthase (eNOS) produces superoxide instead of NO. Vitamin C prevents this uncoupling.

Scholarly Studies: A single-blind RCT on post-viral fatigue found that this combination reduced the prevalence of fatigue from 80.1% (placebo) to 8.7% (active group) after 28 days.<sup>1</sup>  
Dosage: 1.66 g L-Arginine + 500 mg Liposomal Vitamin C, twice daily.

Schedule: Continuous/Daily. Pulse dosing is ineffective here due to the rapid half-life of NO; the endothelium requires constant substrate availability.<sup>1</sup>

## **3. Ginkgo Biloba (EGb 761)**

**Efficacy Rank:** Moderate-High (Cognitive & Rheological Support)

Mechanism of Action:

EGb 761 improves blood rheology (flow properties) and protects mitochondria. It antagonizes Platelet-Activating Factor (PAF), reducing microthrombi formation without the hemorrhage risk of stronger anticoagulants.

Scholarly Studies: Clinical series show restoration of concentration and reduction of "brain fog" within 6 months of daily use.<sup>1</sup>

Dosage: 80 mg per dose, twice daily (Total 160 mg).

Schedule: Continuous/Daily.

## **4. Coenzyme Q10 (Ubiquinol)**

**Efficacy Rank:** Moderate (Bioenergetics)

Mechanism of Action:

Ubiquinol transports electrons in the mitochondrial respiratory chain, facilitating ATP production. It is depleted in post-viral fatigue syndromes.

Scholarly Studies: Studies in rehabilitation settings show Ubiquinol increases plasma CoQ10, improves physical performance, and reduces oxidative stress markers (TBARS).<sup>1</sup>

Dosage: 100 mg twice daily.

Schedule: Continuous/Daily.

## 5. Essential Oil Aromatherapy (Thyme, Orange, Clove, Frankincense)

**Efficacy Rank:** Moderate (Sensory/Limbic Modulation)

Mechanism of Action:

Direct stimulation of the olfactory bulb modulates the limbic system, influencing fatigue perception and mood.

Scholarly Studies: RCTs demonstrate significant reductions in fatigue scores and improved vigor with twice-daily inhalation.<sup>1</sup>

Dosage: Inhalation twice daily.

Schedule: Pulse Dosing (14 days ON / 14 days OFF). This schedule is mandated by the physiology of olfactory receptors, which desensitize (fatigue) rapidly upon constant exposure. The "OFF" period restores sensitivity.<sup>1</sup>

## 6. Echinacea, Rosehip, & Propolis (OFS)

**Efficacy Rank:** Moderate (Immunomodulation)

Mechanism of Action:

Modulates cytokine expression and reduces CRP.

Scholarly Studies: RCTs show significant improvements in quality of life and inflammatory markers after 60 days.<sup>1</sup>

Dosage: 2 capsules daily.

Schedule: Bi-Monthly (2 Months ON / 1 Month OFF). Continuous use leads to immune acclimation; the "OFF" month prevents tolerance.<sup>1</sup>

# Chapter 4: Emergency and Reactionary Protocols

Despite the preventative nature of the main protocol, seniors may experience acute symptom flares or unwanted reactions. The following herbs should be kept "on-hand" for immediate deployment.

## The Emergency Kit

- **Ginger (*Zingiber officinale*)**
  - **Indication:** Sudden nausea, gastric distress, or acute inflammatory pain.
  - **Usage:** Chewable or tea form immediately upon symptom onset. It acts rapidly on gastric 5-HT3 receptors to quell nausea without the sedation of antihistamines.<sup>1</sup>
- **Lavender (*Silexan / Essential Oil*)**
  - **Indication:** Acute anxiety, panic, or agitation spikes.
  - **Usage:** Oral capsule (80 mg) or inhalation. Use as a "rescue" agent for anxiety instead of reaching for a benzodiazepine. It is non-sedating and acts within minutes

via inhalation.<sup>1</sup>

- **Peppermint (*Mentha x piperita*)**
  - **Indication:** Sensory distortions (parosmia flares), tension headaches, or sudden fatigue crashes.
  - **Usage:** Inhalation or topical application to temples. It activates TRPM8 channels to provide a "cooling" distraction from pain and a sharp sensory reset for distorted smell.<sup>1</sup>

## Conclusion

This report establishes a comprehensive framework for the geriatric management of post-acute sequelae, prioritizing the replacement of high-risk synthetic pharmacotherapy with evidence-based natural interventions. By adhering to the **Overlapping Chronopharmacological Schedule**, treating physicians and patients can target the triad of endothelial dysfunction, neuroinflammation, and mitochondrial failure with precision.

The protocol moves beyond simple supplementation. It employs **L-Arginine and Vitamin C** to rebuild the vascular engine, **Ginkgo Biloba** to secure cerebral perfusion, and **PEA-Luteolin** to fundamentally resolve neuroinflammation via the ALIA mechanism. The use of specific substitution matrices for "Double Drug" profiles ensures that the transition from Western medicine is safe, logical, and mechanistically sound. With the rigorous application of these sets—respecting their continuous, cyclical, or pulsed nature—seniors can achieve a restoration of homeostatic health that synthetic polypharmacy often precludes.

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