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The GLP-1 Neurorecovery Paradigm: Implications for Post-intensive Care Syndrome and Mental Health Recovery

João Rêgo Araújo[1], Amália Cinthia Meneses Rêgo[2] and Irami Araújo Filho[3]

[1]Medical Student, School of Medicine, Universidade Potiguar – UnP, Natal, RN, Brazil
[2]Full Professor of Biotechnology, Universidade Potiguar – UnP, Natal, RN, Brazil
[3]Full Professor, Department of Surgery, Federal University of Rio Grande do Norte – UFRN, Natal, RN, Brazil

[*]**Corresponding Author:** Irami Araújo Filho, Full Professor, Department of Surgery, Federal University of Rio Grande do Norte – UFRN, Natal, RN, Brazil

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Abstract

Critical care prevents death far better than it restores function, leaving a growing group of survivors with cognitive, psychiatric, and physical disability—the post-intensive care syndrome (PICS). Its most disabling dimension is cognitive impairment, accompanied by mood and trauma-related symptoms; no current therapy is disease-modifying. A single mechanism increasingly ties these outcomes together: persistent neuroinflammation, wherein blood-brain barrier breakdown, sustained microglial activation, NLRP3-inflammasome signaling, mitochondrial failure, and complement-mediated synaptic loss drive long-term morbidity. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), developed for metabolic disease, act on these exact nodes. Across independent models, semaglutide, tirzepatide, liraglutide, dulaglutide, and exenatide lower neuroinflammation, shift microglia toward repair, protect the barrier, restore bioenergetics, and support synaptic plasticity. The mechanistic case is strongest for cognition, where complement-mediated synaptic loss is a defined target; any benefit for psychiatric symptoms would plausibly be a downstream consequence of reduced neuroinflammation. We bring these previously separate literatures together to propose the GLP-1 Neurorecovery Paradigm: the hypothesis that GLP-1 RAs are candidate neuroimmunometabolic therapies able to modify cognitive recovery after critical illness. The evidence base that bears on PICS specifically consists of experimental models and observational human data; no interventional clinical study of any kind has evaluated a GLP-1 RA in ICU survivors, and the negative phase 3 exenatide, evoke, and evoke+ trials counsel caution. The framework is therefore biologically plausible but clinically unproven. We set out the biomarker, mechanistic, observational, and randomized studies needed to test it.

Key Words: critical illness; delirium; glucagon-like peptide-1 receptor agonists; neuroinflammation; post-intensive care syndrome; sepsis-associated encephalopathy

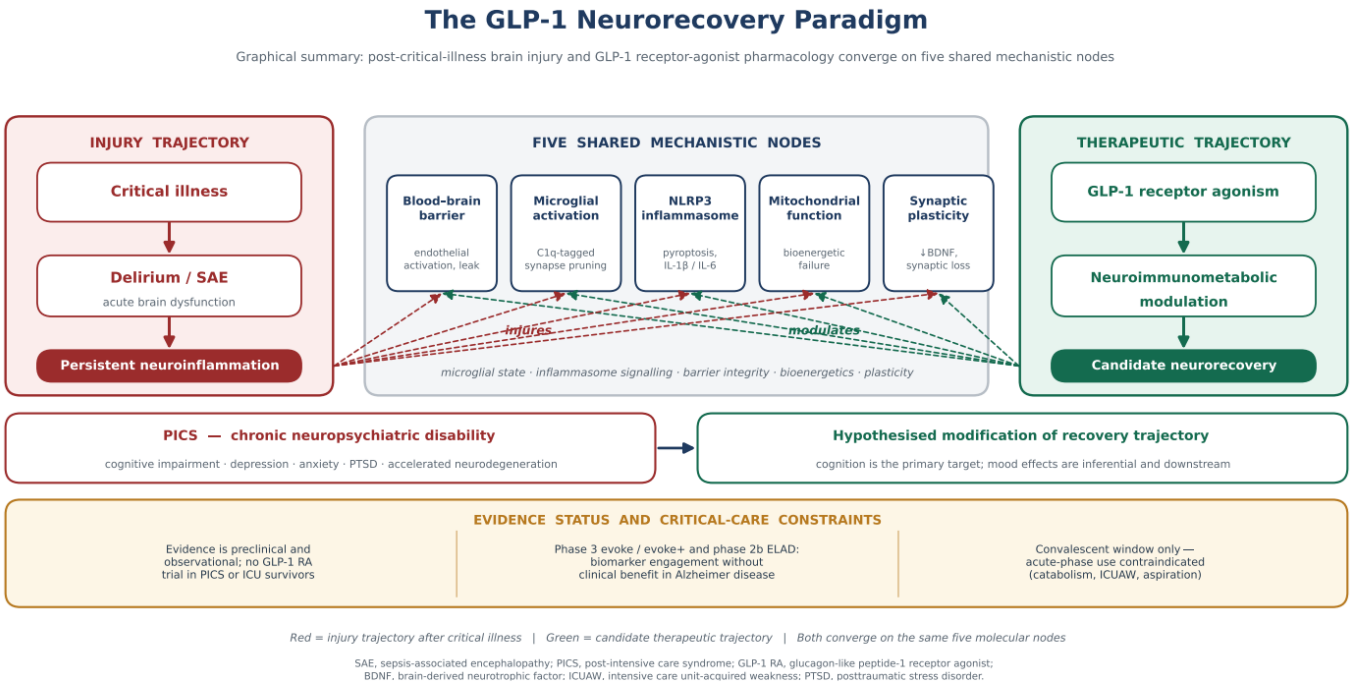
Key Messages

Post-intensive care syndrome carries a heavy, underrecognized neuropsychiatric burden—cognitive impairment, depression, anxiety, and posttraumatic stress disorder—for which intensive care unit and postdischarge care remain supportive rather than disease-modifying.

Persistent neuroinflammation—blood-brain barrier disruption, microglial activation, NLRP3-inflammasome signaling, mitochondrial failure, and synaptic loss—is a unifying, targetable mechanism linking critical illness to long-term cognitive and psychiatric disability.

The proposed GLP-1 Neurorecovery Paradigm reframes GLP-1 receptor agonists as candidate neuroimmunometabolic therapies for recovery after critical illness—a biologically plausible but unproven hypothesis that calls for biomarker-enriched, convalescent-phase trials.

In the PICS setting the supporting evidence is confined to experimental models and observational human data; no randomized, controlled, or otherwise interventional clinical study has tested a GLP-1 receptor agonist in ICU survivors. Every therapeutic statement in this article should be read at that evidentiary level.



Graphical Abstract

Introduction

Critical care has become very good at preventing death. Lung-protective ventilation, balanced resuscitation, timely source control, and protocolized sepsis care now carry patients through insults that were routinely fatal a generation ago, and more people leave the intensive care unit (ICU) alive each year. That success has changed the question rather than answered it. Many survivors never get their old lives back. In one prospective cohort followed for three years after ICU-treated sepsis, a striking proportion remained functionally dependent, and much of that new disability was neither pulmonary nor muscular but cognitive [1]. The clinician's responsibility, in other words, no longer

ends at ICU discharge; it now extends into months and years of cognitive and psychological morbidity that acute care neither anticipates nor treats.

We call this syndrome PICS, the post-intensive care syndrome: new or worsening impairment in cognition, mental health, or physical function that begins with critical illness and persists afterward [2,3]. Of its three domains, the neuropsychiatric one is the most disabling and the hardest to treat. Survivors report failing memory, slowed thinking, and trouble with planning and attention, often alongside depression, anxiety, and posttraumatic stress disorder (PTSD); in sepsis survivors, posttraumatic symptoms can wax and wane for at least two years rather than resolve on their own [4].

Depression and anxiety after sepsis are common, tend to travel together, and correlate with circulating markers of immune activation [5,6]. Delirium, once dismissed as a transient nuisance of the critically ill, is now understood as a warning sign of later cognitive decline and death [7,8]. Pooled data confirm that neurologic complications during sepsis predict worse long-term cognition [9], and that recovery, when it happens, is slow, partial, and very uneven between patients [10]. With populations aging and critical illness becoming more common, PICS has quietly grown into a public-health problem: a large group of survivors left newly vulnerable to cognitive and psychiatric disability that we can describe but cannot yet modify.

What links these outcomes is increasingly thought to be persistent, maladaptive neuroinflammation. Sepsis-associated encephalopathy (SAE), the acute brain dysfunction that accompanies systemic infection, has become the reference model for how inflammation in the body injures the brain, and its mechanisms converge on a surprisingly small set of cellular events [11]. Activation of the cerebral endothelium and breakdown of the blood-brain barrier (BBB) let cytokines, damage-associated molecular patterns, and immune cells reach the neuropil [12], where microglia take over as the principal effector cell [13]. Beyond releasing neurotoxic cytokines, activated microglia do something more specific: they prune working connections. In experimental SAE they engulf C1q-tagged synapses and produce measurable cognitive deficits, which recasts postsepsis cognitive impairment as a problem of pathological synaptic loss rather than vague "toxic" injury [14]. NLRP3-inflammasome activation and microglial pyroptosis amplify the process [15], and alarmins such as HMGB1 carry the signal that strips synapses and degrades memory [16]. Beneath it all sits a bioenergetic failure. Mitochondrial dysfunction and oxidative stress in neurons and glia both license inflammasome activity and starve the energy supply that plasticity demands [17]. Plasticity falters and repair stalls; when plasticity is rescued directly in preclinical SAE, cognition recovers, which marks it as a modifiable endpoint rather than a fixed deficit [18].

This program does not switch off when the infection clears. Sepsis-surviving animals show long-lasting, P2X7-dependent neuroinflammation and cognitive impairment well after the acute insult resolves [19], and systemic sepsis hastens Alzheimer-type pathology and chronic glial activation in vulnerable brains [20]. Central injury markers, amyloid-β and caspase-1 among them, rise with sepsis severity [21], and survivors settle into a state of persistent inflammation, immunosuppression, and catabolism that can sustain immunometabolic disturbance both peripherally and centrally [22].

A single thread therefore runs through these patients: critical illness opens the barrier and ignites neuroinflammation; sustained microglial activation, inflammasome signaling, and mitochondrial failure strip synapses and blunt plasticity; the clinical result is cognitive impairment and psychiatric illness—depression, anxiety, PTSD—and, in those already at risk, accelerated neurodegeneration and lasting disability. Seen this way, PICS is not a grab-bag of unrelated deficits but the chronic neuropsychiatric face of a neuroimmunometabolic injury.

Our therapeutics have not kept pace with this understanding. Almost everything we offer for PICS is supportive: follow-up clinics, cognitive and physical rehabilitation, psychological therapy, and attention to nutrition [23]. None of it touches the underlying neuroimmune process. The few attempts to interrupt the cascade pharmacologically have largely failed; in the MIND-USA trial, antipsychotics for ICU delirium changed neither survival nor long-term outcomes, a reminder that quieting symptoms is not the same as protecting the brain [24]. So, the field is left with a wel-

l-mapped, mechanistically coherent injury and no agent that engages it.

That gap is what makes glucagon-like peptide-1 receptor agonists (GLP-1 RAs) worth a second look from the intensivist. Built for type 2 diabetes and obesity, they are now understood as pleiotropic drugs whose reach extends well past glucose and weight [25], and a sizable preclinical and translational literature lands squarely on the pathways that drive post-critical-illness brain injury. GLP-1 receptors sit on microglia and neurons, and activating the central receptor directly dampens Toll-like-receptor-driven inflammation [26], which makes these drugs a brake on the very signaling that defines SAE. In model after model they lower neuroinflammation [27], push microglia from a proinflammatory toward a reparative state [28], and block NLRP3-inflammasome activation while cognition improves [29]. Semaglutide curbs A1-astrocyte conversion and protects the BBB after ischemia [30]; liraglutide tempers astrocytic neuroinflammation [31] and, most relevant to our setting, eases postoperative cognitive impairment through NRF2/NLRP3 signaling [32] and blunts delirium-like behavior in aged surgical animals by restoring microglial mitophagy [33]. The same drugs restore mitochondrial bioenergetics [34], enhance autophagy [35], support neurogenesis [36], and raise brain-derived neurotrophic factor [37], acting on neuroinflammation, microglial state, neuroprotection, plasticity, and mitochondrial function at once. Tirzepatide, a dual GIP/GLP-1 agonist, carries the antineuroinflammatory and antioxidant effects further in early work [38]. Human signals are beginning to appear: a post hoc analysis of EXSCEL found that a GLP-1 RA lowered inflammatory proteins linked to Alzheimer's disease [39], and large psychiatric syntheses report favorable effects on mood and anxiety with no excess suicidality [40,41].

None of this licenses overstatement. The best clinical evidence still comes from metabolic and neurodegenerative disease, and it is mixed: the phase 3 trial of exenatide in Parkinson's disease was negative [42], and the pivotal cognitive trials in Alzheimer's disease [have since reported without demonstrating clinical benefit [43,85,86]. Most of the neuroprotection data come from animal models of uncertain relevance to human PICS, the human associations are largely uncontrolled, and we do not know what central exposure or dose a critically ill patient would need. These are limits on what can be claimed, not reasons to dismiss the hypothesis; they set the research agenda.

What no one has done is bring these two literatures together. The contemporary record holds two mature but separate bodies of work: one on the neuroimmunometabolic pathology of sepsis, SAE, delirium, and PICS, the other on the neuroprotective and neuroimmunomodulatory pharmacology of GLP-1 RAs in metabolic, neurodegenerative, and psychiatric disease. [Despite rapidly expanding evidence for the neuroprotective and neuroimmunomodulatory effects of GLP-1 receptor agonists, no review connects this drug class to PICS, to mental-health recovery after critical illness, or to cognitive recovery after sepsis, and none has proposed a framework that joins them.

We argue that the overlap between these fields is not accidental but mechanistically grounded, and we name it the GLP-1 Neurorecovery Paradigm. The paradigm treats GLP-1 RAs not as glucose-lowering drugs with incidental brain effects, but as neuroimmunometabolic modulators that act on the very nodes—microglial activation, inflammasome signaling, BBB integrity, mitochondrial bioenergetics, and synaptic plasticity—through which critical illness inflicts lasting neuropsychiatric harm. If PICS is the chronic expression of a neuroimmunometabolic insult, then GLP-1 RAs are, almost uniquely among available drugs, able to engage that insult at several points simultaneously. The paradigm reframes the goal from managing symptoms to changing the biological trajectory.

The central hypothesis of this review follows directly: GLP-1 receptor agonists may represent a new class of neuroimmunometabolic therapies capable of modifying the trajectory of cognitive and psychiatric recovery after critical illness. We advance it as a hypothesis to be tested, not a conclusion; its worth lies in the specific, falsifiable predictions it generates.

Our aim, then, is to build and stress-test the GLP-1 Neurorecovery Paradigm by joining the mechanisms of post-critical-illness brain injury to the neuroprotective pharmacology of GLP-1 RAs, to weigh supporting and contradictory evidence even-handedly, and to set out the translational and clinical research needed to learn whether a fa-

miliar metabolic drug class can help restore the minds of those who survive critical illness. A concise visual synthesis of the argument is provided as the Graphical Abstract.

Evidence Sources and Selection Strategy

This article is conceived as a perspective and hypothesis, not as a systematic review, and it was neither registered in PROSPERO nor conducted according to PRISMA. Rather than cataloguing a field, it advances a falsifiable argument: that two mature but largely separate bodies of evidence—the neuroimmunometabolic pathology of critical illness and the neuroprotective pharmacology of GLP-1 receptor agonists—converge closely enough to constitute a testable therapeutic hypothesis. Because the transparency of a hypothesis-generating review depends on how its evidence was assembled, we describe that process explicitly.

We searched PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library from database inception to July 2026, and screened ClinicalTrials.gov and the EU Clinical Trials Register for completed and ongoing interventional studies. Four thematic blocks of terms were combined with the Boolean operator AND, with terms within each block combined with OR, using controlled vocabulary (MeSH/Emtree) and free-text variants: (i) *clinical setting*—"critical illness", "sepsis", "septic shock", "intensive care", "ICU survivor", "post-intensive care syndrome", "sepsis-associated encephalopathy", "delirium"; (ii) *mechanism*—"neuroinflammation", "microglia", "NLRP3", "inflammasome", "blood-brain barrier", "mitochondrial dysfunction", "synaptic plasticity", "complement", "neurofilament light chain"; (iii) *intervention*—"GLP-1", "glucagon--like peptide-1 receptor agonist", "incretin", "semaglutide", "liraglutide", "tirzepatide", "exenatide", "dulaglutide"; and (iv) *outcome*—"cognition", "cognitive impairment", "neuroprotection", "depression", "anxiety", "posttraumatic stress disorder", "quality of life". The search was supplemented by backward and forward citation tracking of key articles and by hand-searching the reference lists of relevant reviews. No date or design restriction was applied; screening was limited to records with an English-language full text or abstract.

Records were screened by title and abstract and then in full text against a single criterion: whether the study informed either the mechanistic architecture of post-critical-illness brain injury or the neuro-relevant pharmacology of GLP-1 receptor agonism. Priority was given, in descending order, to randomized clinical trials and systematic reviews or meta-analyses, to prospective human cohorts, and to mechanistic preclinical work addressing one or more of the five nodes around which the paradigm is built. Studies were retained irrespective of the direction of their findings, and null, negative, and discordant results—most importantly the phase 3 exenatide trial in Parkinson disease, the evoke and evoke+ trials, the ELAD trial, and the GDF15 data that run counter to the hypothesis—were deliberately kept in view and are cited explicitly, precisely because an attractive new framework invites confirmation bias.

Two limitations of this approach should be stated plainly. First, no formal risk-of-bias appraisal and no quantitative synthesis were undertaken, because the heterogeneity of designs, species, models, agents, and outcome measures rules out meaningful pooling. Second, the final citation set was selected to be representative and argument-bearing rather than exhaustive; other investigators applying the same searches would legitimately retain a different, overlapping set of articles. The value of the synthesis therefore lies not in completeness but in the specific, refutable predictions it generates and in the research agenda it defines.

The Neuropsychiatric Legacy of Critical Illness

In modern critical care, survival and recovery have come apart. Patients who would once have died now leave the ICU carrying a neuropsychiatric burden the acute illness neither predicted nor resolved [1]. Three years on from ICU-treated sepsis, many remain functionally dependent, and the dependence is disproportionately cognitive and psychological [1]. When survivors are followed over time, their cognitive courses diverge—sepsis survivors do worse than other ICU survivors, and modifiable exposures such as benzodiazepine sedation track with poorer outcomes—a finding that makes at least part of post-critical-illness cognitive injury iatrogenic, and therefore partly preventable [10,44]. Posttraumatic symptoms can run a fluctuating, multiyear course [4], and depression and anxiety are frequent, usually comorbid, and increasingly seen as something to screen for rather than stumble upon [5,6,45].

This triad of new cognitive, psychiatric, and physi-

cal impairment that outlasts discharge is PICS [3]. Its overlap with postsepsis syndrome and the postacute sequelae of COVID-19 hints at a shared biology of inflammatory brain injury rather than three separate diseases [2], an idea supported by the persistent cognitive slowing and neuroaxonal injury seen in COVID-19 survivors [46,47]. Yet PICS is still routinely missed. It falls between specialties and slips past the acute metrics by which we judge our ICUs, often surfacing only when a patient cannot return to work or is started on a new psychiatric drug months later [48]; cognitive reserve hides it further in higher-functioning people [49]. The consequence is a growing population newly prone to cognitive decline, mood and trauma-related disorders, and accelerated neurodegeneration—people for whom everything we currently offer is supportive and nothing is disease-modifying.

Neuroinflammation as a Unifying Mechanism After Critical Illness

The simplest account of this convergence is a shared substrate: persistent, maladaptive neuroinflammation. SAE has become the working model for how inflammation in the periphery damages the brain, and its mechanisms collapse onto a limited set of cellular events with notable consistency [11]. Systemic inflammation activates the cerebral endothelium and degrades the BBB, with endothelial TREM-1 signaling helping cytokines, alarmins, and immune cells cross into the neuropil [12,50]; microglia then take over as the effector cell and the hub onto which otherwise diverse insults converge [13,51].

What matters most is the specificity of the injury. In experimental SAE, activated microglia eat complement--tagged synapses and leave lasting cognitive deficits, which reframes postsepsis cognitive impairment as targeted synaptic loss rather than diffuse toxicity [14]. NLRP3-inflammasome activation and microglial pyroptosis spread the damage, with several regulatory nodes—TRIM45, OTUD1, and HDAC3/STING—feeding the same axis [15,52,53], while HMGB1 and related alarmins carry out the synaptic stripping that erodes memory [16]. The cytokine load matters too: IL-1β, IL-6, TNF-α, and IFN-γ disturb neural oscillations and drive neurodegeneration through microglial nitric oxide and oxidative stress [54,55,56]. Underneath sits bioenergetic failure, in neurons, glia, and even circulating platelets, which simultaneously permits inflammasome activation and removes the fuel that synaptic maintenance requires [17,57]. Plasticity suffers as a result; yet restoring plasticity directly rescues cognition in preclinical SAE, which again marks it as a tractable target [18,58].

Three observations move neuroinflammation from bystander to candidate driver. First, it outlives the infection: sepsis-surviving animals show long-lasting, purinergic-receptor-dependent neuroinflammation and cognitive impairment [19]. Second, sepsis accelerates Alzheimer-type pathology and sustained glial activation in vulnerable brains, connecting an acute infection to long-term neurodegenerative risk [20,21]. Third, the inflammation is systemic as well as central; survivors enter a state of persistent inflammation, immunosuppression, and catabolism that can keep immunometabolic disturbance alive along the adipose–brain axis [22,60].

A single chain therefore links critical illness to disability: barrier breakdown and neuroinflammation; sustained microglial activation, inflammasome signaling, and mitochondrial failure; synaptic loss and blunted plasticity; cognitive and psychiatric illness; and primed neurodegeneration. Whether neuroinflammation is the central driver or simply the dominant node in a multifactorial network is unsettled, and the heterogeneity of inflammatory subphenotypes warns against monocausal thinking [61]. [It should also be stated at the outset that this entire chain has been assembled from experimental models and from observational human cohorts: the mechanistic steps are demonstrated almost exclusively in rodents, and the human evidence linking them to PICS outcomes is associative rather than interventional. Even so, it is the most promising shared target we have, and it is exactly the target GLP-1 pharmacology engages. Table 1 summarizes these nodes, their mediators, the candidate GLP-1 receptor-agonist action at each, and the level of evidence currently supporting that action.

Table 1: Mechanisms of neuroinflammation in post-intensive care syndrome and their candidate GLP-1 receptor-agonist targets

Mechanistic node	Key mediators / events in SAE–PICS	Functional consequence	Candidate GLP-1 RA action	Evidence level supporting the GLP-1 action
Blood–brain barrier disruption	Endothelial activation, TREM-1 signaling, tight-junction breakdown; entry of cytokines, DAMPs, immune cells	Neurovascular leak; exposure of neuropil to systemic inflammation	Preservation of barrier integrity; limitation of A1-astrocyte conversion after injury	Preclinical only (rodent ischemia models); no human data in critical illness
Microglial activation	M1 polarization; complement (C1q)-tagged synapse elimination; sustained reactivity	Pathological synaptic pruning; persistent cognitive deficits	M1→M2 repolarization; reduced complement-mediated pruning	Preclinical only; no human imaging or histological confirmation
NLRP3 inflammasome	Pyroptosis; IL-1β, IL-6, TNF-α, IFN-γ; HMGB1/TLR amplification; TRIM45, OTUD1, HDAC3/STING nodes	Sterile inflammatory amplification; neuronal injury	Inflammasome suppression; downstream cytokine reduction with cognitive improvement	Preclinical, plus indirect human biomarker signal from a post hoc analysis of a cardiovascular outcome trial
Mitochondrial dysfunction	Bioenergetic failure and oxidative stress in neurons, glia, platelets; impaired mitophagy	Loss of substrate for synaptic maintenance; licensing of inflammasome	Restoration of mitochondrial bioenergetics; enhanced autophagy/mitophagy	Preclinical, summarized in systematic reviews of non-ICU models
Synaptic plasticity / neurotrophic failure	Synaptic loss; reduced BDNF and neurogenesis; arrested repair	Impaired learning, memory, executive function	Upregulation of BDNF; promotion of neurogenesis and plasticity	Preclinical, summarized in systematic reviews; no human cognitive benefit demonstrated in completed trials
Immunometabolic dysregulation	Persistent inflammation–immunosuppression–catabolism; adipose–brain axis	Sustained systemic and central inflammatory tone	Immunometabolic modulation; attenuation of hyperglycemia-driven neuroinflammation	Human evidence in metabolic disease; extrapolated—not tested—in critical illness survivors

[a] SAE: sepsis-associated encephalopathy; [b] PICS: post-intensive care syndrome; [c] GLP-1 RA: glucagon-like peptide-1 receptor agonist; [d] DAMP: damage-associated molecular pattern; [e] BDNF: brain-derived neurotrophic factor. GLP-1 RA actions are derived predominantly from preclinical models; none has been tested in human PICS. The final column is provided in response to the need to make the evidentiary level explicit at every node: no entry in this table rests on interventional clinical data obtained in ICU survivors.

GLP-1 Receptor Agonists as Neuroimmunometabolic Agents

GLP-1 RAs were built for metabolic disease, but the weight of evidence now makes "purely metabolic" untenable as a description [25]. The receptor is present on neurons and glia, and central GLP-1R activation directly suppresses Toll-like-receptor-driven inflammation, placing these drugs upstream of the innate-immune signaling that starts SAE [26,62]. Across models they reduce neuroinflammation and nudge microglia toward a reparative phenotype [27,28]—the same nodes that define post-critical-illness brain injury.

A mechanism easy to overlook for an enterocrine hormone is the gut-brain axis. Native GLP-1 is released by intestinal L cells and acts substantially through GLP-1 receptors on vagal afferent terminals, relaying enteric and immune signals to the nucleus tractus solitarius and onward to hypothalamic and limbic circuits; this vagal-brainstem route complements direct central receptor activation and engages the cholinergic anti-inflammatory pathway, a recognized brake on systemic and neural inflammation [26,68]. For the critically ill—in whom gut barrier failure, dysbiosis, and vagal dysautonomia are common—this axis is not a peripheral curiosity but a plausible conduit through which GLP-1 receptor agonism could dampen the neuroinflammatory signaling that drives sepsis-associated encephalopathy, and it may help explain central effects that exceed what blood-brain barrier penetrance alone would predict.

Read drug by drug, the picture holds together. Semaglutide blocks NLRP3-inflammasome activation while cognition improves, shifts microglia from M1 to M2, targets osteopontin-expressing microglia to limit perioperative stroke injury, and curbs neurotoxic A1-astrocyte conversion while protecting the BBB after ischemia [29,28,63,30]. The barrier protection appears to be active repair rather than passive sparing: in preclinical models GLP-1 receptor activation upregulates the endothelial tight-junction proteins claudin-5, occludin, and zonula occludens-1 and suppresses matrix metalloproteinase-9, restoring paracellular sealing through PI3K/Akt signaling and reduced oxidative and VEGF-driven permeability [30]. Liraglutide is the most directly relevant to our setting: it reduces postoperative cognitive impairment through NRF2/NLRP3 signaling and dampens delirium-like behavior in aged surgical animals by restoring microglial mitophagy—about as close to the clinical problem as preclinical work gets [32,33]—and it also reshapes astrocyte polarization and limits vascular and neuronal injury in mixed models [31,64]. Tirzepatide extends the antineuroinflammatory and antioxidant effects [38,65]; exenatide shows immune-resolving actions through spinal microglial β-endorphin/IL-10 signaling [66]; and dulaglutide has been argued, on mechanistic grounds, to share the class's neuroprotective potential [67]. The shared machinery is consistent: GLP-1 RAs restore mitochondrial bioenergetics, enhance autophagy, support neurogenesis, and raise brain-derived neurotrophic factor through identifiable brainstem GLP1R–BDNF circuits [34,35,36,68], a convergence on glial biology coherent enough to be reviewed as one pharmacology [69]. The early human signals run the same way: a post hoc EXSCEL analysis showed lower circulating Alzheimer-associated inflammatory proteins [39], and large psychiatric syntheses report favorable or neutral—though modest and heterogeneous—effects on mood and anxiety with a reassuring suicidality profile [40,70], plausibly tracking neuroinflammatory modulation rather than weight loss alone, though a primary psychiatric action remains unproven [71,72]. [It bears emphasis that every drug-level statement in this paragraph, with the sole exception of the EXSCEL post hoc analysis and the psychiatric syntheses, derives from animal models.

Table 2 compares the five agents by receptor target, reported CNS-relevant actions, highest level of neuro evidence, and relative central penetrance; the class-level claim rests most firmly on semaglutide and liraglutide, with tirzepatide, exenatide, and dulaglutide more thinly supported. The most consequential clinical data have now arrived, and they demand caution: the phase 3 evoke and evoke+ trials of oral semaglutide in early Alzheimer's disease, reported in 2026, did not slow clinical progression, even though Alzheimer-related and neuroinflammatory biomarkers improved on treatment [43,85]; the phase 2b ELAD trial of liraglutide likewise missed its primary metabolic endpoint while showing supportive secondary signals on brain atrophy and cognition [86]. This dissociation—biological engagement without confirmed clinical benefit—is the central cautionary lesson the paradigm must absorb. No other

available class engages this combination of mechanistic actions, but no trial has yet shown that engaging them changes a hard clinical outcome.

Table 2: Neuroprotective and neuroimmunomodulatory actions of GLP-1 receptor agonists

Agent	Receptor target	Reported CNS-relevant actions	Highest level of neuro evidence	CNS penetrance (relative)
Semaglutide	GLP-1R	NLRP3 suppression with improved cognition; M1→M2 microglial polarization; targeting of osteopontin-expressing microglia in perioperative stroke; reduced A1-astrocyte conversion; BBB protection	Preclinical; [phase 3 Alzheimer disease trials (evoke, evoke+) completed and negative on clinical progression despite biomarker improvement	Moderate (CNS-active formulations under study)
Liraglutide	GLP-1R	Reduced postoperative cognitive impairment via NRF2/NLRP3; attenuation of delirium-like behavior via microglial mitophagy; astrocyte modulation	Preclinical, including surgical/delirium models most relevant to critical care; phase 2b ELAD trial completed, primary endpoint missed	Moderate
Tirzepatide	GIP/GLP-1R (dual)	Antineuroinflammatory and antioxidant effects	Preclinical (early)	Uncertain / under characterization
Exenatide	GLP-1R	Immune-resolving actions via spinal microglial β-endorphin/IL-10 signaling	Clinical in Parkinson disease (phase 3 negative)	Low–moderate
Dulaglutide	GLP-1R	Shared class mechanisms argued on mechanistic grounds	Mechanistic rationale; limited direct neuro data	Low (large molecule)

[a] GIP: glucose-dependent insulinotropic polypeptide; [b] NRF2: nuclear factor erythroid 2-related factor 2; [c] BBB: blood–brain barrier; [d] CNS: central nervous system. CNS-penetrance estimates are approximate and agent- and formulation-dependent; head-to-head human CNS-exposure data are lacking. No agent has been evaluated in PICS or ICU-survivor cognitive recovery.

Could GLP-1 Receptor Agonists Modify the Trajectory of PICS?

The question that matters is whether this pharmacology can be turned from metabolic and neurodegenerative disease toward recovery after critical illness. The case is best made by laying the GLP-1 profile over the SAE/PICS cascade one node at a time. For persistent neuroinflammation, central GLP-1R-mediated TLR inhibition and NLRP3 suppression hit the two upstream events that start and sustain SAE [26,29], with the potential to break a self-feeding loop that supportive care never reaches [19]. For cognitive decline, the drugs' support of neurogenesis, BDNF signaling, and mitochondrial bioenergetics targets the synaptic and metabolic substrate whose failure underlies postsepsis impairment [34,36,68]. Most provocatively, by restraining the complement-dependent synapse elimination that produces deficits in SAE [14], a GLP-1 RA could tip the balance from pathological pruning back toward preservation. For psychiatric outcomes the claim must be the most guarded: the reported antidepressant and anxiolytic signals are modest and largely associative, and are best read as a downstream, inferential consequence of reduced neuroinflammation rather than evidence of a primary psychiatric effect; the mechanistic weight of this paradigm rests on cognition, not mood [5,71,72]. The metabolic angle is not a distraction either: acute hyperglycemia worsens neuroinflammation and cognition in SAE, so the glycemic and immunometabolic actions of these drugs may add to, rather than dilute, any neuroprotection [73].

This case has to be disciplined by what cuts against it, and the human record is sobering. The phase 3 exenatide trial in Parkinson's disease was negative [42]; the phase 3 evoke and evoke+ trials of semaglutide in early Alzheimer's disease did not slow clinical progression despite improving neuroinflammatory and disease biomarkers [85]; and the phase 2b ELAD trial of liraglutide missed its primary metabolic endpoint [86]. Taken together, these results show that engaging the mechanistic nodes—even demonstrably, at the level of biomarkers—has not yet translated into a hard clinical benefit in neurodegenerative disease, and central exposure differs from agent to agent [74].

The biology has internal tension, too: GDF15, a mediator partly engaged by GLP-1-associated pathways, itself worsens sepsis-induced cognitive impairment, and GDF15 and semaglutide act through largely separate routes—so the incretin–stress-cytokine interface is not uniformly benign [75,76]. Most important, no study has tested a GLP-1 RA in PICS, in ICU survivors, or in human sepsis-associated cognitive recovery; the closest evidence, the liraglutide delirium and postoperative-cognition models, is suggestive but neither clinical nor PICS-specific [32,33]. [The asymmetry is worth stating in one line: the mechanistic case is strong, internally consistent, and almost entirely preclinical; the human case is entirely inferential.

THE GLP-1 Neurorecovery Paradigm

These observations support a reframing we call the **GLP-1 Neurorecovery Paradigm**: GLP-1 receptor agonists are neuroimmunometabolic modulators that act on the shared mechanistic nodes—microglial activation and polarization, NLRP3-inflammasome signaling, blood-brain barrier integrity, mitochondrial bioenergetics, and synaptic plasticity—through which critical illness produces lasting cognitive and psychiatric injury, and therefore stand as candidate disease-modifying agents for neurorecovery after critical illness. It joins two trajectories that have been studied apart: the pathological one, running from critical illness through neuroinflammation and neuroimmune dysfunction to cognitive impairment, psychiatric sequelae, and disability; and the therapeutic one, running from GLP-1 receptor agonism through neuroimmunomodulation and neuroprotection to plasticity and recovery. The claim is that the two meet at identifiable molecular nodes, densely enough to count as a testable hypothesis rather than a loose analogy. Figure 1 maps this convergence, showing the red injury trajectory of critical illness and the green candidate therapeutic trajectory of GLP-1 receptor agonism meeting on five shared molecular nodes; the Graphical Abstract presents the same convergence in condensed form, together with the evidentiary caveats that bound it.

It departs from current thinking in three ways. It is mechanistic rather than symptomatic: where PICS care today supports patients as they decline, the paradigm proposes to engage the biology of the decline. It is deliberately pleiotropic rather than single target: most experimental neuroprotectants in SAE address one node [15,53], whereas this approach rests on partial, simultaneous modulation of several interacting nodes, which better fits an injury that is itself distributed. And it is ready for repurposing, since it redirects a well-characterized drug class with a known safety profile, shortening the usual distance from mechanism to trial. It remains, explicitly, a framework for generating and organizing hypotheses, not a claim of proven efficacy.

Clinical and Translational Implications for the Intensivist

The target populations are easy to name. ICU and sepsis survivors carry both the heaviest neuropsychiatric burden and the strongest mechanistic rationale [1,10]; delirium survivors form an enriched high-risk subgroup [45]; and older patients with existing metabolic disease, obesity, or diabetes—already candidates for [GLP-1 RAs—offer the most favorable benefit-to-risk balance and the most feasible route to real-world target-trial emulation [59]. Yet the same physiology that makes these survivors a rational target also imposes hard constraints, and these deserve to be stated plainly rather than buried among the opportunities.

The Catabolic Paradox: Sarcopenia, ICU-Acquired Weakness, and Safety Constraints

The central safety problem is a paradox at the heart of the paradigm. The drugs proposed to protect the brain are, by design, agents of weight loss—and the patients in question are already wasting. ICU-acquired weakness (ICUAW), sarcopenia, and progressive muscle catabolism

are not incidental to PICS; they are among its defining features, and they share the inflammatory and mitochondrial drivers that this paradigm seeks to interrupt. GLP-1 receptor agonists lower body weight partly by suppressing appetite and energy intake, and in a patient already losing lean mass this is a concrete hazard, not a theoretical one.

We therefore state the constraint in the strongest terms: administering GLP-1 RAs during the acute, catabolic phase of critical illness should be regarded as contraindicated. Three converging risks make acute phase use untenable. First, accelerated lean-mass loss: superimposing a potent anorexiant on the catabolic, anabolic-resistant state of acute critical illness could deepen the very muscle wasting that drives long-term disability [77,78]. Second, aspiration: delayed gastric emptying is directly dangerous in sedated, ventilated, or recently extubated patients, and may also impair enteral nutrition and the absorption of coadministered medication [79]. Third, ICUAW itself, which GLP-1–associated catabolic stress could compound during the period of maximal vulnerability.

These constraints do not refute the paradigm; they bound it, and they translate into firm design principles. Timing is paramount: any future trial must target the convalescent window exclusively—after the acute catabolic phase has resolved and anabolic resistance is lifting—never the early ICU course (Figure 2).

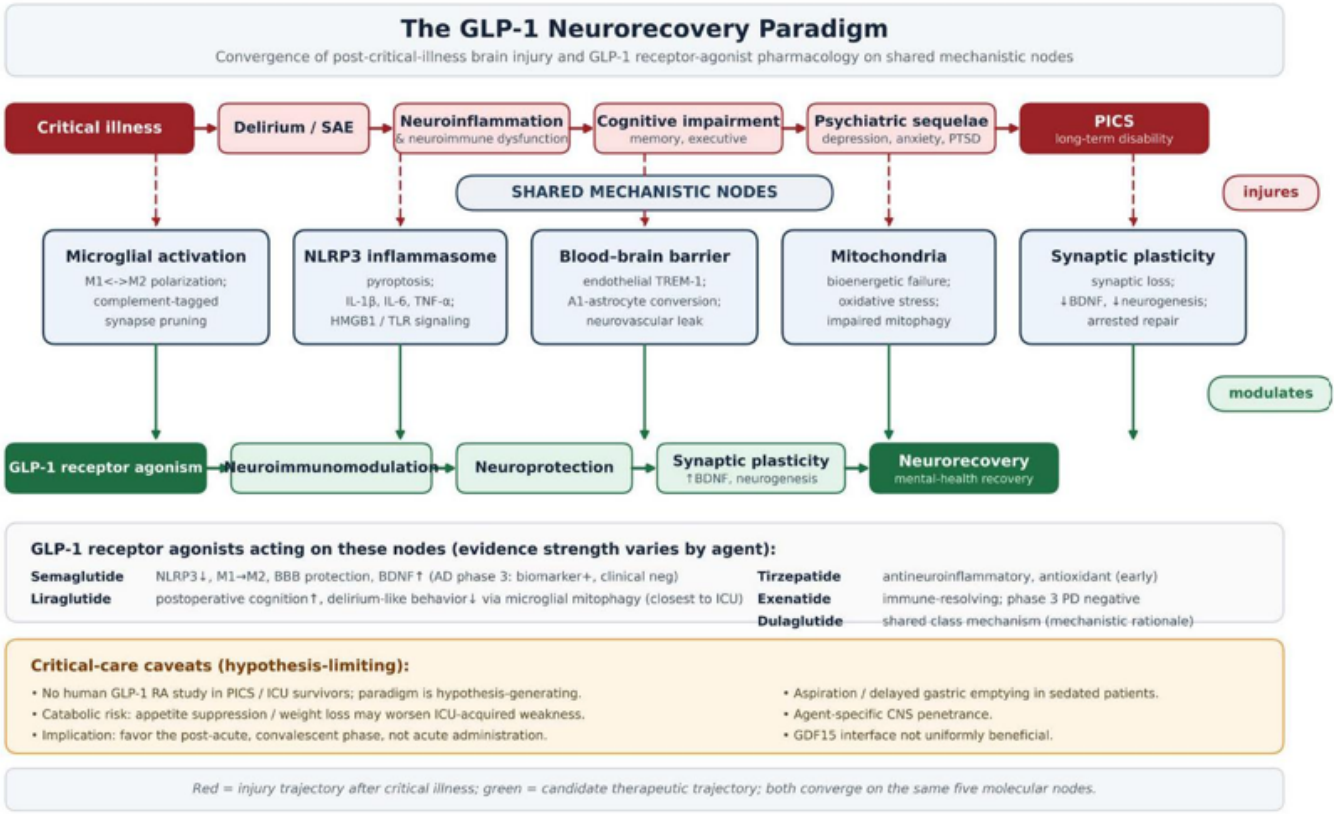


Figure 1: The GLP-1 Neurorecovery Paradigm.

Patient selection must be phenotype-driven: the rational population for first-in-PICS testing is the survivor with obesity or type 2 diabetes, in whom these agents are already indicated and in whom lean-mass concerns are attenuated. Co-intervention and monitoring are not optional: trials should pair the drug with protein-target nutrition and resistance-based rehabilitation and should track lean mass directly (ultrasound or bioimpedance) with muscle preservation as a coprimary safety endpoint.

Pharmacokinetics add a further caution: the severe subcutaneous edema and anasarca common in critical illness and early convalescence can erratically alter the absorption and bioavailability of subcutaneously administered

agents, which should inform the choice of agent, formulation, and route. Renal function is a final determinant of safety, because acute kidney injury and renal replacement therapy are common in PICS survivors; although these peptides are degraded largely by peptidases rather than renally cleared, impaired metabolite handling and heightened vulnerability to volume depletion and gastrointestinal fluid losses warrant cautious dosing and close monitoring. Finally, cost and access are not trivial for a frequently vulnerable survivor population, and any eventual benefit must be weighed against equitable availability. Table 3 maps these constraints onto a staged research agenda, from mechanistic confirmation to a convalescent-phase, biomarker-enriched phase 2 trial with lean-mass safety embedded throughout.

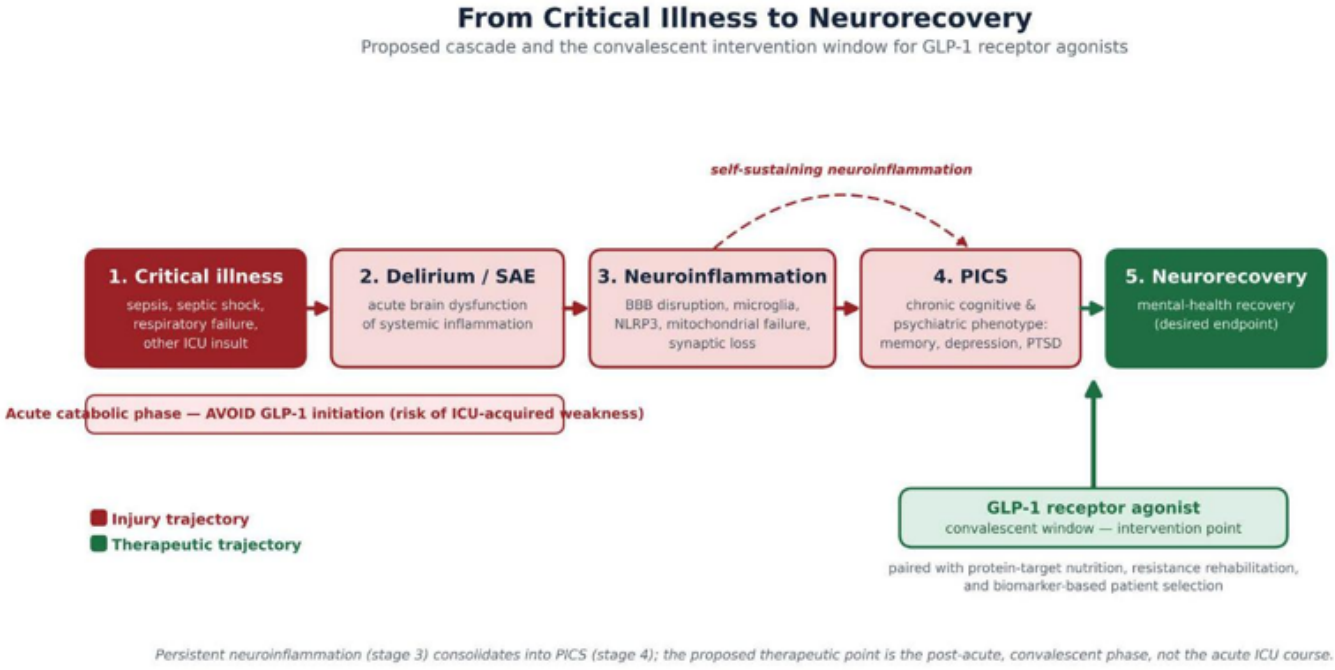


Figure 2: Proposed cascade from critical illness to neurorecovery and the convalescent intervention window.

Research Gaps and Future Directions

The agenda follows from how inferential the case still is. Mechanistic work should establish CNS target engagement in models of critical illness specifically and characterize agent-specific BBB penetrance along with effects on microglial phenotype, complement-mediated pruning, and inflammasome activity in validated SAE and PICS models, including apelin-responsive and standardized murine systems 80,81]. Biomarkers are a priority: neurofilament light chain and CSF chemokines could mark neuroaxonal injury and neuroinflammation, enrich trial populations, and serve as pharmacodynamic readouts, while inflammatory subphenotyping could pick out the likely responders [61,47,82,6]. Neuroimaging adds structural, functional-connectivity, and barrier-permeability endpoints, building on cohorts already assembled in survivors [83,84]. Observational and pharmacoepidemiologic studies, especially target--trial emulations in diabetic and obese ICU survivors already taking these drugs, could generate confirmatory signals while controlling for confounding [59]. The definitive step is randomized trials—biomarker-enriched, started in the convalescent phase, powered for patient-centered cognitive and psychiatric outcomes, and watchful of lean-mass safety.

Route of administration deserves explicit study. The systemic agents used today are given subcutaneously and reach the brain only to the extent that they cross the blood-brain barrier, which differs by molecule and is incompletely characterized; intranasal delivery, by contrast, exploits olfactory and trigeminal nose-to-brain transport to reach the central nervous system while largely bypassing the barrier and the periphery, and could in principle raise central exposure and the local neuroprotective effect—while lowering the systemic, appetite-suppressing dose that drives the catabolic risk most relevant to critically ill survivors.

Whether intranasal GLP-1 delivery achieves meaningful, safe central target engagement in this population is an open and testable question.

Table 4 summarizes the clinical trials that currently define the landscape. None of them was conducted in ICU survivors, and the recurring pattern they display—biomarker engagement without a positive primary clinical endpoint—is the single most important external check on the paradigm.

Table 3: Current evidence, knowledge gaps, and future research priorities for the GLP-1 Neurorecovery Paradigm

Domain	What is established	Key knowledge gap	Priority next study (design, population, endpoint)
Mechanism	GLP-1 RAs modulate microglia, NLRP3, BBB, mitochondria, plasticity in non-ICU models [(preclinical evidence only)	CNS target engagement in validated SAE/PICS models is unproven	Mechanistic studies in standardized SAE models; agent-specific BBB penetrance and microglial-phenotype readouts
Biomarkers	NfL and CSF chemokines mark neuroaxonal injury/neuroinflammation (observational human evidence)	No pharmacodynamic biomarker validated for GLP-1 neuro-effect in survivors	Biomarker-anchored cohort linking NfL/cytokine trajectories to cognitive outcome; inflammatory subphenotyping
Neuroimaging	Survivor cohorts show structural/connectivity and barrier changes (observational human evidence)	No imaging readout of GLP-1 effect after critical illness	Imaging substudy (structural, functional connectivity, BBB permeability) nested in a trial
Observational	GLP-1 RAs widely used in diabetes/obesity, incl. ICU survivors	Confounding by indication; no causal estimate for neurorecovery	Target-trial emulation in diabetic/obese ICU survivors on GLP-1 RAs; cognitive/psychiatric outcomes
Interventional	Class is safe and characterized in metabolic disease (no interventional data in PICS)	No RCT in PICS; optimal timing/agent unknown	Phase 2 RCT: convalescent-phase initiation, biomarker-enriched, lean-mass safety co-primary; cognition and mood endpoints

[a] NfL: neurofilament light chain; [b] CSF: cerebrospinal fluid; [c] SAE: sepsis-associated encephalopathy; [d] PICS: post-intensive care syndrome; [e] RCT: randomized controlled trial. Priorities are ordered from mechanistic confirmation toward definitive interventional testing; lean-mass and aspiration safety should be embedded at every interventional stage.

Table 4: Recent and ongoing clinical trials of GLP-1 receptor agonists relevant to neurorecovery

Trial / program	Agent (route)	Population	Primary endpoint	Status & results (2026)	Relevance to PICS
evoke (NCT04777396)	Oral semaglutide 14 mg	Early symptomatic Alzheimer disease (MCI/mild, amyloid+)	Change in CDR-SB at week 104	Completed; negative on clinical progression, AD/neuroinflammatory biomarkers improved 85]	Largest test of GLP-1 disease modification in cognition; biomarker–clinical dissociation is a key cautionary signal

evoke+ (NCT04777409)	Oral semaglutide 14 mg	Early AD including cerebral small-vessel pathology	Change in CDR-SB at week 104	Completed; negative on clinical progression, biomarkers improved [85]	Extends the cautionary signal to a vascular-comorbid population relevant to ICU survivors
ELAD (liraglutide phase 2b)	Liraglutide (subcutaneous)	Mild–moderate Alzheimer disease, non-diabetic	Change in cerebral glucose metabolism (52 wk)	Completed; primary missed; supportive secondary signals on brain atrophy and cognition [86]	Closest GLP-1 agent to the ICU context; biological/structural effect without confirmed primary benefit
Exenatide phase 3 (Parkinson disease)	Exenatide (subcutaneous)	Parkinson disease	MDS-UPDRS motor score	Completed; negative [42]	Tempers extrapolation from preclinical neuroprotection to human disease modification
Target-trial emulation (proposed)	Any GLP-1 RA (subcutaneous)	Diabetic/obese ICU survivors already on a GLP-1 RA	Cognitive and psychiatric outcomes	Not yet conducted	Feasible near-term observational route to a first hypothesis-confirming signal in survivors

[a] CDR-SB: Clinical Dementia Rating–Sum of Boxes; [b] MCI: mild cognitive impairment; [c] AD: Alzheimer disease; [d] MDS-UPDRS: Movement Disorder Society–Unified Parkinson's Disease Rating Scale; [e] PICS: post-intensive care syndrome; [f] GLP-1 RA: glucagon-like peptide-1 receptor agonist. No completed or ongoing trial has evaluated a GLP-1 RA in PICS or ICU-survivor cognitive recovery; the neurodegenerative trials are included to show the current clinical landscape and the recurring lesson that biomarker engagement has not yet produced a positive primary clinical endpoint.

Strengths and Limitations of the Current Evidence

The most important limitation is one of evidentiary level, and it should be stated before any other. Nothing in this article rests on interventional clinical evidence obtained in the population it concerns. The mechanistic architecture of post-critical-illness brain injury is established almost entirely in experimental models—predominantly rodent models of sepsis, SAE, and postoperative cognitive dysfunction—while the human evidence in PICS is observational: prospective and retrospective cohorts, secondary analyses of trials conducted for other purposes, and pharmacoepidemiologic association studies, all of them vulnerable to confounding by indication, healthy-user and immortal-time biases, and residual confounding by the metabolic improvements that accompany treatment. No randomized, controlled, or single-arm interventional study has administered a GLP-1 receptor agonist to an ICU survivor for a neurocognitive or psychiatric outcome. Readers should therefore treat every therapeutic proposition in this article as a hypothesis derived from experimental and observational data, and not as clinical evidence of benefit.

The evidence is strong where it converges: independent groups keep implicating the same microglial, inflammasome, mitochondrial, and synaptic nodes in post--critical-illness brain injury and independently show GLP-1 modulation of those nodes. The limitations are equally real. The literature is dominated by preclinical and mechanistic work, and translation from animal to human has a poor track record here: the exenatide Parkinson's trial and, more pointedly, the semaglutide evoke and evoke+ and liraglutide ELAD trials in Alzheimer's disease were all negative on their primary clinical endpoints, even where biomarkers moved in the expected direction [42,85,86]. Heterogeneity across designs, methods, and species rules out quantitative pooling.

Human associations are largely uncontrolled and open to confounding by indication, healthy-user and immortal-time biases, and the metabolic improvements that

come with treatment, all of which make a direct neural effect hard to isolate. Publication bias probably exaggerates how consistent the preclinical signal looks, central bioavailability differs by agent and is poorly defined [74], and there is, at present, no PICS-specific clinical trial of any kind. [The literature search underpinning this synthesis was narrative rather than systematic, and no formal risk-of-bias appraisal was performed; the citation set is representative rather than exhaustive. We have kept null and discordant findings in view throughout, precisely because an attractive new framework invites confirmation bias.

Conclusions

PICS marks the limit of an acute-illness mindset: we have learned to keep the brain alive through catastrophe without learning how to help it recover. The neuroinflammatory–immunometabolic account of post-critical-illness brain injury now gives us a coherent target, and the fact that a mature, safe, widely used drug class acts on that same target is too specific to wave away. The GLP-1 Neurorecovery Paradigm should be read as a structured, falsifiable hypothesis, not a verdict. Its supporting evidence is experimental and observational, and it awaits its first interventional test in survivors. Its value is not in any premature promise that incretin drugs will rescue the surviving brain—the evidence is still inferential and the contrary signals are real—but in its capacity to organize a fragmented field, name the exact points where mechanism and therapy meet, and yield the specific predictions that good clinical science can test. If those predictions survive mechanistic, observational, and finally randomized scrutiny, a drug class built for metabolic disease may prove among the first that can change the neuropsychiatric trajectory of survival. If they do not, the disciplined effort to find out will still have taught us why the surviving brain so often fails to recover.

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