

# Dose Escalation Strategy and Safety Observation of Neurogenesis-regulating Drugs in Phase I Clinical Trials for Alzheimer's Disease

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**How to cite this paper:** Qingyu Bai. (2025) Dose Escalation Strategy and Safety Observation of Neurogenesis-regulating Drugs in Phase I Clinical Trials for Alzheimer's Disease. *International Journal of Clinical and Experimental Medicine Research*, 9(6), 614-618.  
DOI: 10.26855/ijcemr.2025.11.005

**Received:** September 30, 2025  
**Accepted:** October 28, 2025  
**Published:** November 27, 2025

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## Abstract

Developing Phase I trials for Alzheimer's therapeutics that target neurogenesis requires customized approaches to dosing and safety. This research addresses the challenge by proposing a unified framework built on model-informed design, dynamic biomarker assessment, and specialized evaluation of central nervous system safety. Insights from clinical data analysis are applied to key methodological considerations, including the determination of a first-in-human dose, PK/PD model-driven optimization of subsequent doses, and safety protocols that integrate neurophysiological surveillance with the management of potential long-term carcinogenic effects. The objective is to provide a methodological guide for advancing such innovative drugs through early-stage clinical testing.

## Keywords

Alzheimer's disease; dose escalation; pharmacokinetics; pharmacodynamics

Alzheimer's disease represents a progressive neurodegenerative disorder characterized by distinct pathological hallmarks, most notably neuritic plaques composed of  $\beta$ -amyloid deposits and neurofibrillary tangles resulting from hyperphosphorylation of tau protein. The clinical manifestations of the disease present as a characteristic cognitive impairment syndrome, encompassing progressive memory deterioration, executive function decline, and visuospatial ability deficits, along with a spectrum of psychological and behavioral symptoms [1]. Currently available treatments - including cholinesterase inhibitors and NMDA receptor antagonists - provide only temporary relief of cognitive symptoms without addressing the fundamental progression or modifying the core pathological trajectory of the disease. In recent years, therapeutic strategies targeting the modulation of endogenous neurogenesis have emerged as a promising approach with significant potential. These neurogenesis-modulating drugs precisely intervene to regulate the vital processes of neural progenitor cells in the hippocampal dentate gyrus's subgranular zone, processes that include proliferation, differentiation, migration, and synaptic integration. These interventions aim to structurally repair damaged neural circuits, theoretically granting them the potential to serve as disease-modifying therapies [2]. However, translating these drugs from laboratory research to practical clinical application requires overcoming complex methodological challenges. This necessitates, first, the development of optimized dosage calibration strategies based on computational modeling that comprehensively considers both the penetration dynamics across the blood-brain barrier and the pharmacodynamic characteristics of neural stem cell surface receptors. Second, it requires establishing a comprehensive, multidimensional safety assessment framework capable of monitoring and detecting both acute neuropsychiatric effects and long-term changes in synaptic plasticity that may result from treatment.

Therefore, this study aims to bridge this gap by integrating specialized dosing escalation strategies for neurogenesis-modulating drugs with neural circuit function evaluation protocols. The ultimate objective is to generate robust and balanced medical evidence that enables weighing the expected therapeutic efficacy of these promising drugs

against their associated potential risks, thereby contributing to accelerating their development and safe application for the benefit of Alzheimer's disease patients.

## 1. Theoretical Basis and Technical Framework of Dose Escalation Strategies

### 1.1 Biological Rationale for Dose Escalation

The design of dose escalation strategies for neurogenesis-modulating drugs must be rooted in a deep and integrated understanding of their mechanism of action at the molecular, cellular, and system levels. Contemporary research highlights how the biological effects of these therapeutic agents are closely related not only to the density of specific receptors on neural stem cells but also to the activation thresholds of downstream signaling pathways and the functional state of the hippocampal niche microenvironment.

As demonstrated by the fundamental study by Tuominen R.K. [3], agonists of the TrkB receptor exhibit a complex biphasic dose-response relationship, in which low or physiological concentrations optimally promote the proliferation of neural precursors, while higher doses may paradoxically induce phenomena of aberrant differentiation and morpho-functional alterations. This non-linear pharmacodynamic profile underscores the criticality of a particularly narrow therapeutic window, a distinctive characteristic of many neurotrophic factors and their synthetic analogs. From a pharmacokinetic perspective, the active transport mechanisms of the blood-brain barrier exert a determining influence on the cerebral distribution of these therapeutic agents. Advanced drug delivery systems, such as antibody-mediated transport targeting the transferrin receptor, enable specific targeting to the central nervous system. However, the saturable kinetics of these biological vectors necessitate particularly careful evaluation of the non-linear relationship between receptor occupancy, transport rate, and systemic drug exposure during the definition of the dosing regimen. Integrated PBPK and PD models are therefore essential for predicting the optimal human dosage based on preclinical data.

A fundamental aspect of importance, although often overlooked, concerns the fact that the functional integration of newborn neurons within existing hippocampal circuits requires a finely regulated neurochemical and trophic microenvironment. Consequently, the pharmacological dosage must be calibrated with sub-therapeutic precision not only to maximize the neurogenic potential but also to minimize the risk of aberrant synaptic remodeling, ectopic integration, or altered network excitability - complications that could compromise cognitive function rather than enhance it. This requirement mandates the implementation of *in vivo* monitoring using advanced functional imaging techniques and electrophysiological recordings during the early phases of human clinical studies.

### 1.2 Methods for Designing Dose Escalation Protocols

Traditional dose-escalation designs such as the "3+3" protocol are demonstrating growing limitations in evaluating neurogenesis-modulating compounds due to inherent constraints in statistical efficiency and precision. These conventional approaches, relying on deterministic rules and fixed cohort sizes, exhibit suboptimal adaptability to the complex nonlinear pharmacology characterizing these innovative therapies. Consequently, the clinical development landscape is decisively shifting toward model-informed precision dosing strategies within the Model-Informed Drug Development paradigm.

Recent methodological advances have established the Bayesian logistic regression model as a superior statistical framework capable of dynamically integrating preclinical data with emerging clinical observations. This approach enables real-time estimation of the risk-benefit profile for new dose levels, optimizing decision-making throughout the escalation process [4]. To address the characteristic biphasic dose-response relationship of these compounds - where different doses may produce qualitatively distinct effects—the continuous reassessment method proves particularly valuable. Through sophisticated mathematical modeling, CRM permits adaptive reallocation of patients across different dose cohorts, maximizing exposure within the optimal therapeutic window despite its narrow range.

In the specific context of Alzheimer's disease, the pioneering work of Sharma L [5] demonstrated how adaptive dosing regimens, personalized according to individual characteristics including hippocampal volume and APOE genotype, can significantly reduce inter-individual variability in treatment response. This therapy personalization represents a crucial advancement for maximizing therapeutic efficacy while minimizing adverse events. Complementing these approaches, real-time monitoring of neurogenesis-associated biomarkers - including serum BDNF levels and hippocampal perfusion parameters obtained through advanced imaging techniques - provides a solid pharmacodynamic foundation for guiding dose adjustments. The integration of these dynamic biomarkers within Bayesian modeling frameworks enables continuous assessment of the drug's biological effects, transforming the dose escalation process from a primarily empirical exercise to a mechanistically informed and quantitatively robust procedure.

## 2. Multi-Dimensional Construction of the Safety Observation System

### 2.1 Acute Safety Monitoring

Acute safety profiling of neurogenesis-targeting therapeutics necessitates a multidimensional evaluation strategy specifically calibrated for the central nervous system. Evidence suggests these agents are associated with a distinct spectrum of neuropsychiatric adverse effects [6]. In the early stages of treatment, it has been noted that agonists of neurotrophic factor receptors can cause temporary dysfunction in the prefrontal cortex. This is often evident as a reversible drop in scores on standardized tests designed to assess executive functions. These functions encompass a range of high-order cognitive processes, such as planning, decision-making, and impulse control. The reversible nature of this decline suggests that the effects may be transient and potentially reversible upon discontinuation or dose adjustment of the drug.

Electroencephalography studies offer additional valuable insights. Certain small-molecule compounds that modulate neurogenesis, especially when the dosage is being adjusted, lead to a significant surge in theta band power. This alteration in brain electrical activity shows a clear temporal link with patients' subjective reports of experiencing cognitive "fogginess" or a feeling of mental haziness. Theta band activity is typically associated with states of drowsiness, relaxation, or certain cognitive processes like memory retrieval. The increase in theta power in this context may reflect a disruption in normal cognitive functioning, contributing to the patients' perceived cognitive difficulties. From a neurovascular standpoint, new drugs that target the vascular endothelial growth factor pathway carry potential hazards related to the integrity of the blood-brain barrier. The blood-brain barrier is a highly selective semipermeable border that separates the circulating blood from the brain extracellular fluid, protecting the brain from harmful substances in the bloodstream. An early sign of compromised blood-brain barrier integrity is an elevation in vascular permeability. This can be detected non-invasively through dynamic contrast-enhanced magnetic resonance imaging techniques [7]. DCE-MRI involves the injection of a contrast agent and then monitoring its distribution over time in the brain tissue. Changes in the rate and pattern of contrast agent accumulation can indicate alterations in vascular permeability, providing an early warning of potential damage to the blood-brain barrier.

### 2.2 Observation of Long-Term Neuroplasticity Effects

Assessing the enduring consequences of neuroplasticity brought about by drugs that regulate neurogenesis demands the adoption of diverse, multimodal monitoring strategies. These strategies are vital for accurately tracking the ever-changing structural and functional developments within the hippocampus, a region critical for memory and learning. Longitudinal investigations utilizing diffusion tensor imaging have shed light on the fact that individuals receiving neurotrophic factor treatments show dose-related improvements in the integrity of white matter. Specifically, these enhancements are observed in the neural pathways linking the dentate gyrus of the hippocampus and the entorhinal cortex. The significance of these structural modifications extends beyond mere anatomical alterations. They are intricately tied to better performance in episodic memory assessments, suggesting that the strengthened white matter connections may enhance the efficiency of information flow and memory storage within the hippocampal-entorhinal neural circuit [8].

Delving into the molecular realm, repeated analyses of cerebrospinal fluid in treatment-responsive subjects have unveiled a distinct pattern of biomarker fluctuations. On one hand, there is a noted stabilization in the levels of neurofilament light chain, a protein that acts as a barometer for the structural soundness of neurons. This indicates that the treatment aids in preserving the integrity of existing neuronal structures. On the other hand, there is a marked increase in neurogranin, a protein intimately linked to synaptic plasticity and the process of neuroregeneration. The simultaneous presence of stable neurofilament light chain levels and elevated neurogranin implies that the treatment not only spurs the creation of new neurons but also ensures their proper integration and functional development within the pre-existing neural framework. This dual action supports comprehensive neuroregeneration while safeguarding the structural stability of neurons.

## 3. Optimization Strategies for Dose-Safety Balancing

### 3.1 Model-Informed Dose Prediction

Pharmacokinetic/pharmacodynamic modeling plays a pivotal role in the clinical development of neurogenesis-modulating drugs by mathematically quantifying the dynamic relationships between drug exposure, target engagement, and biological effects. For receptor occupancy-response relationships, integrating *in vitro* receptor binding kinetics with *in vivo* microdialysis data enables the construction of quantitative models linking TrkB receptor occupancy to BDNF secretion levels, thereby informing the determination of the minimum effective biological occupancy. To

address the unique pathological environment of Alzheimer's disease, disease-drug interaction models incorporate parameters such as the impact of  $\beta$ -amyloid burden on neurogenesis baseline, enhancing the predictive accuracy for long-term dosing regimens. A study conducted by Zhang J [9] provides further insights into the role of PK/PD modeling. This research utilized physiologically-based pharmacokinetic modeling, a sophisticated approach that takes into account the physiological characteristics of the body. The study found that individual differences in the efflux efficiency of P-glycoprotein, a protein located at the blood-brain barrier that pumps drugs out of the brain, can result in over a three-fold variation in drug exposure within the central nervous system. This variation helps to partially account for the clinical heterogeneity observed in dose-response relationships, where different patients may exhibit varying responses to the same drug dose.

### 3.2 Multicenter Data Sharing and Risk Prediction

Setting up reliable and efficient systems for sharing data across multiple centers and predicting risks is of paramount importance for the safety assessment of drugs that modulate neurogenesis. Centralized repositories specifically designed for recording neurotoxicity incidents play a vital role. These repositories enforce standardized protocols for data collection, ensuring consistency and accuracy. By doing so, they enable real-time, cross-trial analysis of neuropsychiatric adverse events. Research has demonstrated that such well-structured systems can significantly enhance the ability to detect rare adverse events, boosting detection sensitivity by more than threefold. This is crucial because rare adverse events may go unnoticed in individual trials but can become apparent when data from multiple centers are pooled and analyzed collectively.

In the realm of risk prediction, dynamic Bayesian network models have emerged as powerful tools. These models are adept at integrating multiple types of data, including drug exposure levels, the changing patterns of biomarkers over time, and clinical endpoint data. By combining these diverse data streams, the models can generate early warnings regarding potential neurocognitive decline. Simulation studies have provided evidence that these models are capable of accurately predicting severe adverse events up to four weeks before they occur. This early prediction capability allows for timely intervention and adjustment of treatment plans, potentially mitigating the severity of adverse events. Berry D A [10] highlighted the significance of establishing unified risk classification criteria that are specific to each class of neurotrophic agents. Currently, the lack of standardized criteria can lead to inconsistencies in identifying dose-limiting toxicities. By creating drug-class-specific criteria, the efficiency of identifying these toxicities can be greatly improved. This, in turn, comprehensively strengthens the early warning system and enhances risk management strategies for neuropsychiatric adverse events during clinical trials.

## 4. Conclusion

This study systematically establishes an innovative evaluation framework for Phase I clinical trials of neurogenesis-modulating drugs in Alzheimer's disease. By integrating model-informed dose optimization strategies with safety monitoring protocols specifically designed for the central nervous system, we have developed a multidimensional assessment framework that spans from molecular target engagement to neural network function. This system provides methodological guidance for balancing the therapeutic benefits of these drugs against their neuropsychiatric risks, offering significant value for advancing the translation of disease-modifying therapies from preclinical research to clinical application.

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