# Application of Network Pharmacology in the Palliative Management of Neurodegenerative Disorders

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Graphical Abstract

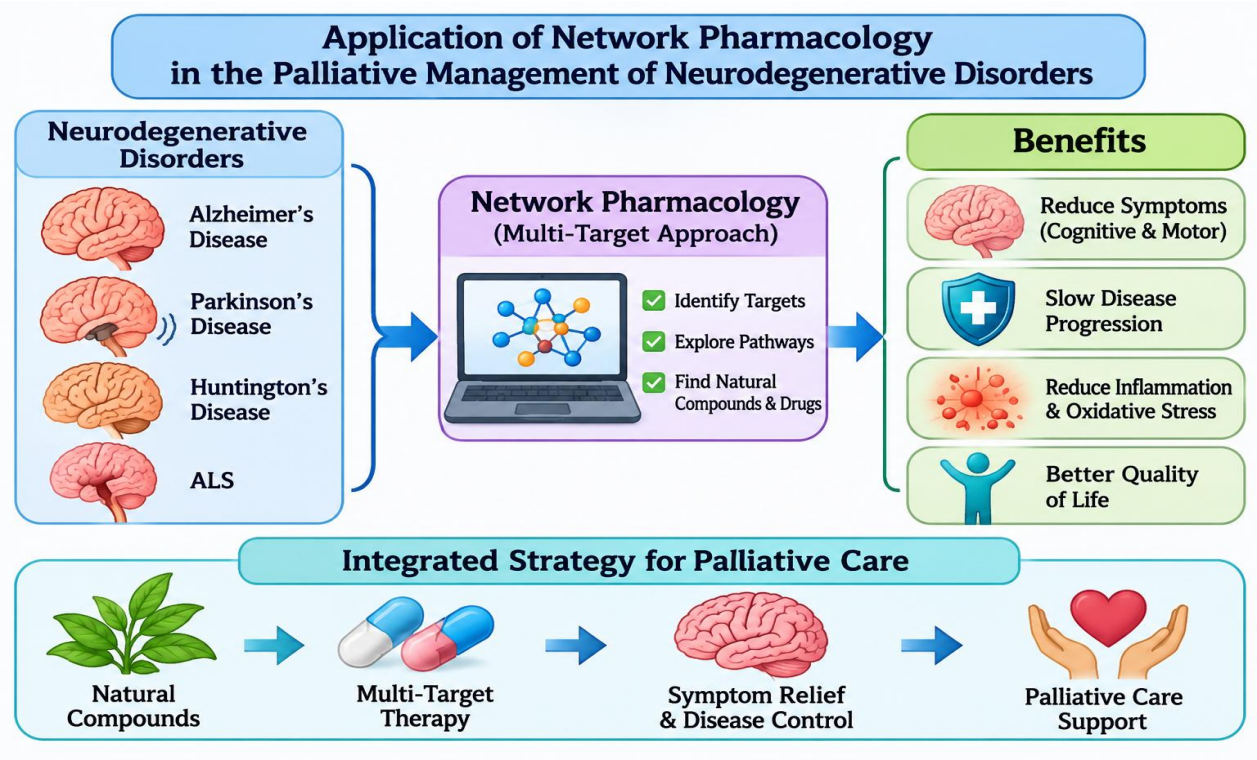



Figure 1. Simplified graphical representation of network pharmacology in the palliative management of neurodegenerative disorders. [1]

***Abstract*—Neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis, are progressive conditions driven by interacting molecular processes such as abnormal protein handling, neuroinflammation, oxidative stress, mitochondrial dysfunction, synaptic failure and altered neurotransmission. Their burden extends beyond neurological impairment and frequently includes pain, sleep disruption, anxiety, depression, fatigue, dysphagia, spasticity, autonomic symptoms, cognitive decline and caregiver distress. Palliative care addresses these**

**multidimensional needs through early, continuous and person-centred symptom relief and is not restricted to end-of-life care. Network pharmacology provides a systems-level framework for examining relationships among compounds, molecular targets, signalling pathways, disease phenotypes and drug combinations. By integrating curated databases, transcriptomic and proteomic evidence, protein–protein interaction networks, pathway enrichment, molecular docking and experimental validation, it may help prioritize multi-target candidates relevant to disease mechanisms and symptom burden. This review discusses the principles and workflow of network pharmacology in neurodegeneration, disease-specific and cross-disease networks, and opportunities for drug repurposing and natural-product research in support of palliative objectives. It emphasizes the distinction between computational prediction and demonstrated clinical benefit. Network pharmacology is not itself a palliative intervention and cannot replace multidisciplinary care. Its potential contribution is to prioritize testable candidates, identify interaction risks and support symptom-oriented therapeutic hypotheses. Limitations include database bias, target-prediction uncertainty, blood–brain barrier constraints, disease-stage effects, polypharmacology-related toxicity and limited clinical validation. A translational framework linking patient-defined needs to reproducible computational analysis, experimental confirmation and patient-centred clinical evaluation is proposed.**

***Index Terms*—Network pharmacology; neurodegenerative disorders; palliative care; Alzheimer's disease; Parkinson's disease; amyotrophic lateral sclerosis; Huntington's disease; systems biology; polypharmacology; quality of life.**

## I. INTRODUCTION

Neurodegenerative disorders comprise conditions characterized by progressive dysfunction and loss of selected neuronal populations. Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) differ in clinical presentation and dominant pathology, yet share biological processes including proteostasis failure, mitochondrial stress, neuroimmune activation and disruption of neuronal communication. These overlapping mechanisms provide a rationale for investigating strategies that address interacting pathways rather than a single molecular target.[2]

The impact of these disorders is not limited to neuronal pathology. Patients may experience pain, rigidity, tremor, gait impairment, constipation, sleep disturbance, mood symptoms, dysphagia, respiratory compromise, communication difficulties and loss of independence. Symptoms vary by diagnosis and disease stage, while patient and caregiver priorities change over time. Palliative care is appropriately integrated early alongside disease-directed treatment, with goals that include relief of suffering, preservation of function, shared decision-making and family support.[11]

Network pharmacology represents drug action as relationships among compounds, proteins, genes, pathways, cells and disease phenotypes. It emerged from recognition that complex diseases and many medicines cannot be adequately described by a one-drug–one-target model. Network analysis can reveal target convergence, pathway crosstalk, repurposing opportunities and potential adverse effects arising from multi-target activity. These features make it relevant to neurodegeneration, although predictions require experimental testing.[3]

A critical distinction is required: palliative care is a clinical model centred on the needs, values and goals of people living with serious illness, whereas network pharmacology is a research methodology for generating mechanistic hypotheses. Network analysis may inform discovery or repositioning of medicines for symptoms or disease-associated biology, but cannot independently establish symptom relief, clinical effectiveness or suitability for an individual. This review examines how these domains can be connected without overstating the evidence.[ 16]

## II. REVIEW SCOPE AND LITERATURE APPROACH

This narrative review synthesizes foundational and recent literature on network pharmacology, systems biology, neurodegenerative mechanisms and neuropalliative care. It includes methodological publications on network construction and target prediction, reviews and primary research on AD, PD, HD and ALS, and clinical literature addressing palliative needs in progressive neurological disease. It is a conceptual narrative synthesis, not a registered

systematic review; it does not claim exhaustive retrieval, formal risk-of-bias scoring or quantitative meta-analysis.[4]

For an applied project, a reproducible search should specify databases, dates, exact search strings, eligibility criteria, study types and duplicate-handling methods. Network studies should report database versions, target-prediction thresholds, identifier mapping, network confidence cut-offs, enrichment background, software versions and validation strategy. Small changes in database content or analytical thresholds can alter network topology and candidate ranking.[18]

## III. BIOLOGICAL COMPLEXITY OF NEURODEGENERATIVE DISORDERS

### 3.1 Shared Molecular Processes

Protein misfolding and impaired proteostasis are central features of several neurodegenerative disorders. Amyloid-β and tau pathology are associated with AD, α-synuclein aggregation with PD, mutant huntingtin with HD, and aggregation of proteins such as TDP-43 or SOD1 with subsets of ALS. Although the proteins differ, cellular consequences may converge on impaired autophagy, proteasomal stress, synaptic dysfunction and neuronal vulnerability. Network analysis can map these proteins to shared regulators while distinguishing common nodes from disease-specific drivers.[8]

Neuroinflammation involves microglia, astrocytes, cytokines, complement components and peripheral immune signals. Glial responses may be protective in some contexts and damaging when persistent or dysregulated. Inflammatory signalling intersects with oxidative stress, mitochondrial dysfunction, blood–brain barrier changes and synaptic pruning. The role of a network node may depend on cell type, disease stage and anatomical region; a highly connected hub is not automatically a safe or beneficial target.[20]

Mitochondrial impairment and oxidative stress recur across neurodegenerative conditions. Reduced energy production, altered calcium handling, reactive oxygen species and defective mitochondrial quality control can amplify neuronal stress. These processes interact with inflammation and protein aggregation, potentially creating self-reinforcing loops. A computational signature of antioxidant or anti-inflammatory activity does not prove adequate brain exposure or clinical efficacy.[22]

### 3.2 Disease-Specific Features

In AD, network investigations commonly examine amyloid precursor protein processing, tau phosphorylation, cholinergic signalling, synaptic plasticity, neuroinflammation, lipid metabolism and vascular contributions. Mechanisms vary among individuals, and clinical phenotype is influenced by age, comorbidities and co-pathologies. Network pharmacology may integrate genetic risk, transcriptomic signatures and compound–target relationships, but candidate interventions should be linked to a defined outcome such as agitation, sleep, pain, appetite or daily function.[7,23]

PD involves degeneration of dopaminergic neurons in the substantia nigra and broader changes in motor, cognitive, autonomic and affective circuits. Relevant networks include α-synuclein biology, lysosomal and autophagy pathways, mitochondrial quality control, dopamine metabolism and neurotransmitter systems beyond dopamine. Palliative needs include motor fluctuations, pain, anxiety, hallucinations, constipation, sleep disturbance, dysphagia and caregiver burden. Candidate research must account for interactions with dopaminergic therapy.[9]

HD is associated with a pathogenic CAG expansion in HTT and widespread effects on transcription, neuronal transport, mitochondrial function and synaptic signalling. ALS involves progressive motor-neuron degeneration, with respiratory, nutritional, communication and psychological consequences. Genetic and molecular subgroups include variants affecting SOD1, C9orf72, TARDBP and FUS. Network analysis may identify convergent stress pathways while preserving distinctions between genetic subtypes and clinical trajectories.[10]

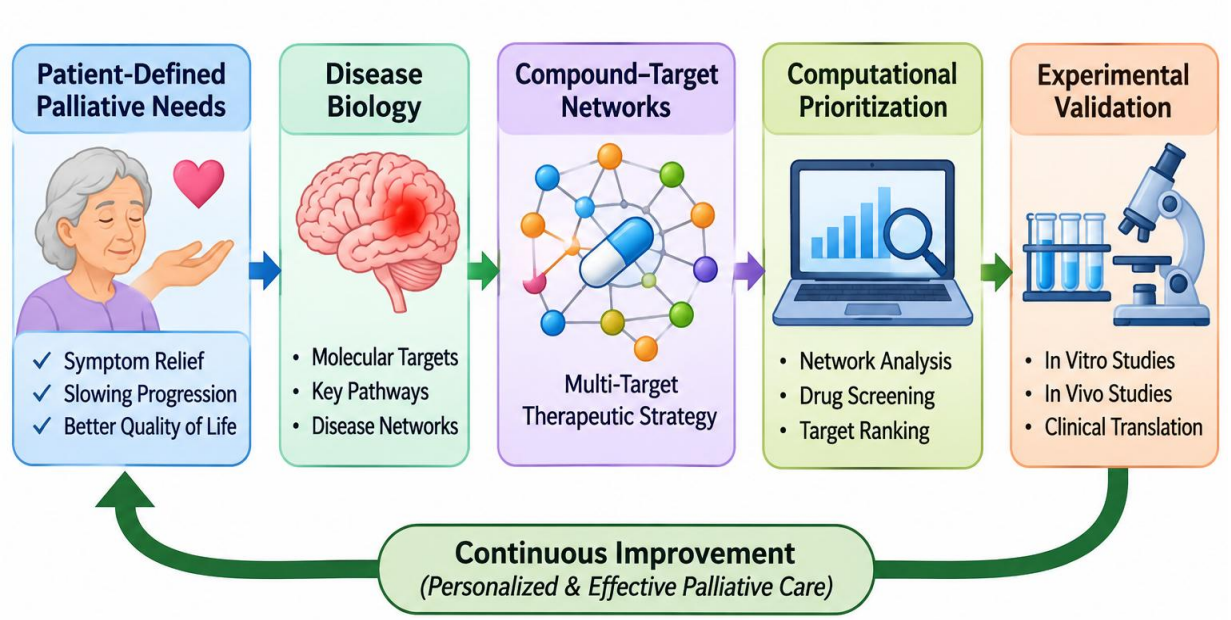



Figure 2. Network pharmacology framework linking patient-defined palliative needs, disease biology, compound–target networks, computational prioritization and experimental validation.[22]

## IV. PRINCIPLES AND METHODOLOGICAL WORKFLOW OF NETWORK PHARMACOLOGY

### 4.1 Compound and Target Collection

An applied workflow begins by defining the intervention and clinical question. Candidate compounds may be derived from approved medicines, investigational drugs, natural products or multi-component formulations. PubChem provides chemical structures and identifiers, while DrugBank, ChEMBL and BindingDB provide drug and bioactivity information. For herbal formulations, resources such as TCMSP can support initial exploration; predicted oral bioavailability or drug-likeness filters are not proof of human exposure, safety or efficacy.[28]

Disease-associated genes and proteins can be assembled from GeneCards, DisGeNET, OMIM and disease-specific repositories, retaining evidence levels and provenance. Lists should be restricted to the disease, tissue, cell type or phenotype relevant to the question. Broad lists may be dominated by generic inflammation or stress terms. Genetic evidence, patient-derived omics, neuropathology and text-mined associations should be distinguished.[32]

### 4.2 Network Construction and Topological Analysis

Compound–target networks connect candidate molecules with reported or predicted protein targets. Protein–protein interaction networks may be assembled using STRING, which integrates experimental, curated, co-expression, genomic-context and text-mining evidence. Cytoscape and related tools support visualization and analysis. Measures such as degree, betweenness, closeness and clustering coefficient describe network structure; they do not independently establish causal importance or therapeutic tractability.[ 35]

Hub proteins are nodes with high connectivity or centrality under a selected network definition. They may represent important regulators, but can also appear prominent because they are extensively studied or broadly expressed. Candidate selection should combine topology with disease-specific evidence, cell-type relevance, direction of change, druggability, safety and clinical plausibility. Sensitivity analysis using alternative confidence thresholds can test whether prioritized nodes remain stable.[18]

### 4.3 Functional Enrichment, Docking and Dynamic Modelling

Gene Ontology and pathway enrichment analyses identify biological processes overrepresented in a candidate gene set. Resources include Gene Ontology, KEGG and Reactome. Results depend on the selected background universe, gene mapping and multiple-

testing correction. Enrichment indicates representation of a pathway, not whether it is activated, inhibited or causally responsible for a clinical symptom.[37]

Molecular docking estimates plausible ligand-binding poses, while molecular dynamics can explore structural behaviour over time. These methods help prioritize compounds, but docking scores are not equivalent to experimentally measured affinity and simulations depend on structural quality, protonation, force fields and sampling. Biochemical assays, target-engagement studies and cellular experiments remain necessary.[40]

4.4 Validation and Reproducibility

Validation should progress from computational predictions to experimental tests. Depending on the hypothesis, this may include receptor or enzyme assays, cell-based pathway measurements, gene perturbation, organoid or animal models, pharmacokinetic assessment and target-engagement biomarkers. For CNS candidates, brain exposure, active metabolites, blood–brain barrier transport and unbound drug concentrations are important. Off-target effects and interactions with medicines used in neurodegenerative disease and palliative care should also be assessed.[17]

Reproducibility requires reporting data sources, access dates, database versions, software versions, identifiers, thresholds, statistical methods and complete candidate lists. Negative or discordant validation results should not be omitted. Natural-product studies require particular attention to botanical identity, chemical standardization, extraction methods, compound identification and exposure data.[16]

## V. CONNECTING NETWORK PHARMACOLOGY WITH PALLIATIVE MANAGEMENT

Palliative care in neurodegenerative disorders involves repeated assessment of physical symptoms, psychological distress, communication, social circumstances, spiritual concerns, caregiver needs and treatment preferences. It may begin at diagnosis or when substantial symptom burden emerges and continue alongside disease-directed treatment. Network pharmacology can contribute indirectly by helping investigate mechanisms underlying symptoms or identify candidate medicines for future testing; it cannot replace clinical assessment, rehabilitation, psychosocial support, advance care planning or multidisciplinary coordination.[13]

A patient-centred research question should identify a symptom or care outcome before selecting molecular targets. Research may investigate neuropathic pain, sleep disruption, anxiety, constipation, spasticity, dysphagia-related complications or neuropsychiatric symptoms. The target network should be assembled using evidence relevant to the symptom, disease, anatomical circuit and stage. This is more clinically meaningful than selecting a compound first and retrospectively assigning a broad neuroprotective rationale.[24]

Drug repurposing may be valuable because approved medicines have established human exposure and safety information, although use in a new population or indication still requires evaluation. A repurposing hypothesis should consider dose, CNS penetration, organ function, frailty, polypharmacy, contraindications and interactions with existing therapy. Multi-target activity may be advantageous but can also increase adverse effects.[15,16]

Natural products and multi-component formulations are frequently investigated because their constituents may interact with multiple targets. Network pharmacology can generate hypotheses about anti-inflammatory, antioxidant, metabolic or neurotransmitter-related activity. However, predicted targets and docking results are not proof of clinical benefit. Botanical identity, chemical standardization, batch consistency, bioavailability, contaminants, herb–drug interactions and controlled clinical evidence must be addressed before palliative use is considered.[29]

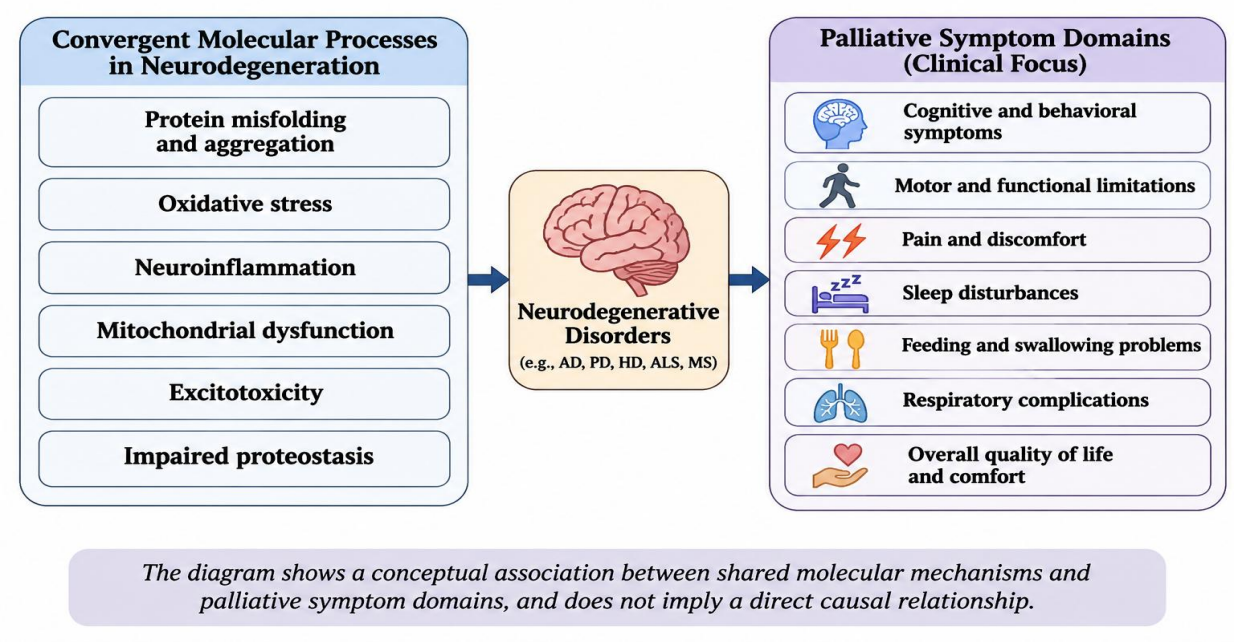



Figure 3. Molecular Mechanisms and Palliative Symptom Domains in Neurodegeneration.[27]

## VI. DISEASE-SPECIFIC PALLIATIVE OPPORTUNITIES

### 6.1 Alzheimer's Disease and Related Dementias

Palliative management in dementia includes assessment and treatment of pain, agitation, anxiety, depression, sleep disturbance, appetite changes, swallowing problems and distress associated with communication or environmental changes. Non-pharmacological approaches, caregiver education and evaluation of reversible causes remain central. Network pharmacology could support research into neuroinflammatory, cholinergic, serotonergic, circadian and pain-related mechanisms, but candidate interventions must be tested for meaningful improvement in comfort or function and for risks such as sedation, falls, delirium and drug interactions.[ 21]

A network-guided dementia programme should not treat cognitive decline as the only outcome. Measures may include pain-related behaviour, sleep quality, agitation frequency, caregiver distress, functional ability and adverse events. Because some patients have difficulty reporting symptoms, validated observational instruments and caregiver-informed assessments may be required. A biomarker change does not necessarily improve lived experience.[12]

### 6.2 Parkinson's Disease and Related Movement Disorders

Palliative care for PD addresses motor fluctuations, rigidity, pain, fatigue, anxiety, depression, hallucinations, sleep disorders, constipation, urinary symptoms, dysphagia and communication difficulties. Network pharmacology may explore interactions among dopaminergic, cholinergic, serotonergic, noradrenergic, inflammatory and mitochondrial pathways. Therapeutic hypotheses must account for medication timing, orthostatic hypotension, cognitive vulnerability and risks of worsening hallucinations or sedation.[14]

Research priorities should include symptom clusters rather than isolated symptoms. Pain may coexist with rigidity, dystonia, sleep disruption and mood symptoms, while fatigue may reflect motor, autonomic, sleep and affective components. Network models can generate hypotheses, but clinical studies should stratify participants by phenotype and assess patient-reported outcomes, function and treatment burden. Neuropalliative literature supports early needs-based care and advance care planning for progressive parkinsonian syndromes.[5]

### 6.3 Huntington's Disease

Palliative needs in HD may include chorea, rigidity, dysphagia, weight loss, psychiatric symptoms,

cognitive impairment, communication difficulty and caregiver stress. Network-guided research could integrate mutant huntingtin-related transcriptional changes with synaptic, mitochondrial, inflammatory and neurotransmitter pathways. Candidate interventions should be evaluated for comfort, swallowing safety, nutrition, behaviour and caregiver burden rather than relying solely on motor scores or molecular readouts. Genetic counselling and family-centred support remain essential.[10,25]

6.4 Amyotrophic Lateral Sclerosis

ALS produces progressive weakness and may lead to respiratory insufficiency, dysphagia, communication impairment, pain, spasticity, sialorrhoea, anxiety and dependence. Palliative care should be integrated early and coordinated with respiratory, nutritional, rehabilitation and communication services. Network pharmacology may investigate molecular subtypes and pathways involving RNA processing, protein homeostasis, excitotoxicity, oxidative stress and neuroinflammation. Clinical relevance depends on whether resulting candidates can safely improve symptoms or reduce treatment burden.[27]

ALS research should incorporate patient priorities regarding non-invasive ventilation, gastrostomy, communication aids, mobility and future care decisions. Studies of symptom-directed candidates need to account for respiratory function, swallowing status, nutritional state, organ function and concomitant medicines. Palliative outcomes may include dyspnoea, pain, secretion management, communication, caregiver strain and goal-concordant care.[26]

Table 1. Major disorders, network themes and palliative-relevant symptom domains[14]

| Disorder | Representative network themes | Palliative needs | Potential research focus |
|---|---|---|---|
| AD/dementia | Amyloid, tau, cholinergic signalling, neuroinflammation | Pain, agitation, sleep, mood, swallowing, caregiver distress | Symptom phenotyping and neuroimmune networks |
| PD | α-synuclein, dopamine, lysosome/autophagy, mitochondria | Pain, motor fluctuations, hallucinations, sleep, constipation | Motor/non-motor clusters and interaction mapping |
| HD | Mutant huntingtin, transcription, synaptic and mitochondrial pathways | Chorea, psychiatric symptoms, dysphagia, weight loss | Genotype-aware models and comfort endpoints |
| ALS | RNA processing, proteostasis, excitotoxicity, oxidative stress | Dyspnoea, secretion, pain, spasticity, nutrition, communication | Genotype-informed networks and symptom candidates |

## VII. SYMPTOM DOMAINS AND NETWORK-LEVEL RESEARCH QUESTIONS

Pain in neurodegenerative disease can be nociceptive, neuropathic, musculoskeletal or related to dystonia and immobility. Network research may examine nociceptive signalling, neuroimmune mediators, ion channels, monoaminergic pathways and descending pain modulation. The objective should be to identify safe adjunctive approaches for defined pain phenotypes, rather than assume that anti-inflammatory or antioxidant network signatures will provide analgesia. Clinical pain assessment and individualized treatment remain essential.[16]

Sleep and mood symptoms may arise from neurodegeneration, medication effects, circadian disruption, immobility, autonomic dysfunction or environmental factors. Network analyses could investigate melatonin-related signalling, monoamine systems, orexin pathways, inflammatory mediators and stress responses. Sedative effects may increase falls, confusion, aspiration risk or daytime somnolence, particularly in frail patients. Research should evaluate symptom benefit and functional safety together.[14]

Spasticity, rigidity, tremor and other motor symptoms involve interactions among basal ganglia, corticospinal, spinal and peripheral systems. Network-guided work may prioritize targets within neurotransmitter, ion-channel and neuroinflammatory networks. For palliative applications, reduction in painful spasms, improved positioning, easier transfers and better sleep may be more relevant than a laboratory measure alone. Rehabilitation, assistive devices and caregiver training should be considered alongside medicines.[24]

Dysphagia, constipation, sialorrhoea, urinary symptoms and nutritional problems arise from autonomic, enteric, bulbar and motor dysfunction. Network pharmacology can generate hypotheses about neurotransmission and neuromuscular control, but clinical management requires assessment of aspiration risk, hydration, nutrition, bowel function and medication effects. A proposed target should be evaluated for the possibility of worsening another symptom domain.[30]

Table 2. Network-pharmacology resources and their roles [28]

| Resource/tool | Primary use | Typical output | Important caveat |
|---|---|---|---|
| PubChem | Chemical identity | Structures and identifiers | Does not establish activity |
| DrugBank / ChEMBL / BindingDB | Drug–target evidence | Known or measured target relationships | Check assay context |
| GeneCards / DisGeNET / OMIM | Disease-associated genes | Gene/protein lists | Evidence quality varies |
| STRING | Protein association network | Interactions with confidence scores | Not all edges are direct binding |
| Cytoscape | Network visualization | Maps and topology metrics | Centrality is not causality |
| GO / KEGG / Reactome | Functional enrichment | Processes and pathways | Depends on background and correction |
| AutoDock / MD tools | Structural hypothesis | Docking poses and trajectories | Requires experimental confirmation |

## VIII. PROPOSED INTEGRATED WORKFLOW FOR NEUROPALLIATIVE RESEARCH

The workflow begins with a clearly stated unmet palliative need and measurable outcome. A multidisciplinary team should define the target population, disease stage, symptom phenotype, existing standard care and clinically meaningful change. Patient and caregiver input is necessary because priorities and acceptable treatment burdens differ. This step prevents computational analysis from becoming detached from the clinical purpose.[31]

Clinical data are then integrated with molecular evidence. Depending on feasibility, this may include transcriptomics, proteomics, metabolomics, genetic data, drug exposure information and published target relationships. Data should be stratified by disease subtype, cell type, brain region and disease stage wherever possible. Candidate compounds can be mapped to targets, and disease- and symptom-associated networks constructed using curated databases and transparent thresholds.[33]

Network topology and pathway analysis prioritize candidate targets, pathways and compounds. The framework should include biological plausibility, evidence strength, druggability, CNS exposure, safety, potential interactions and alignment with the intended symptom outcome. Docking or molecular dynamics may support a binding hypothesis but should not be the sole selection criterion. Alternative network thresholds and independent datasets should test robustness.[34,6]

Experimental validation should use assays selected for the proposed mechanism. These may include target-binding or enzyme assays, neuronal and glial cell models, patient-derived induced pluripotent stem cell systems, organoids, animal models and pharmacokinetic studies. Candidates should be assessed for brain penetration, active metabolites, off-target effects and interactions with commonly used

medicines. Biomarkers should be linked to functional or symptom-related outcomes where possible.[18]

Clinical evaluation should retain a palliative orientation. Outcomes may include pain, sleep, mood, agitation, dyspnoea, swallowing-related complications, function, quality of life, caregiver burden, adverse events and goal-concordant care. A candidate should advance only when expected benefit is proportionate to risks and treatment burden. Network pharmacology can prioritize hypotheses, but patient-centred clinical evidence is required to establish utility.[16]

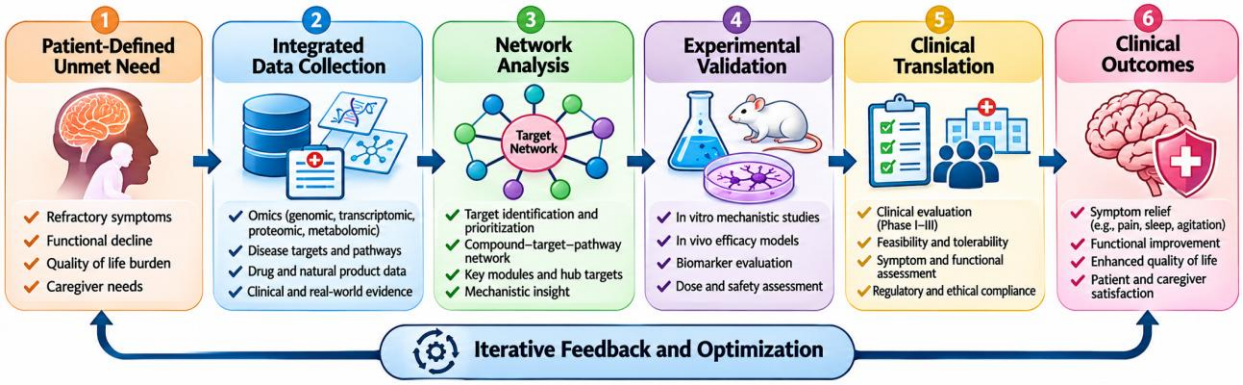



Figure 3. Proposed translational pathway linking a patient-defined unmet need to integrated data, network analysis, experimental validation and clinical outcomes.[34]

## IX. DRUG REPURPOSING AND MULTI-TARGET THERAPEUTICS

Drug repurposing is attractive because development of new CNS medicines is costly and biologically challenging. Network pharmacology can compare known drug targets with disease-associated networks, identify pathway convergence and prioritize medicines for further investigation. Repurposing does not remove the need for dose-finding, safety monitoring or clinical trials: a medicine safe for one indication may be unsuitable in a frail older adult or in combination with dopaminergic, antipsychotic, antidepressant, antiepileptic or analgesic therapy.[15]

Multi-target compounds may be useful where several pathological processes contribute to a phenotype. Natural products and selected synthetic molecules can interact with multiple enzymes, receptors or signalling proteins, potentially producing broader biological effects. Polypharmacology can also create unpredictable toxicity, pharmacokinetic interactions and effects on unrelated pathways. A rational strategy should define intended targets, tolerated activities and off-target effects that could compromise comfort or safety.[1,4]

A palliative lens changes the criteria used to judge candidate value. A modest improvement in pain, sleep, anxiety, secretion control or ease of care may be meaningful even if disease progression is not altered. Conversely, a favourable biomarker change accompanied by confusion, falls, nausea or monitoring burden may have little net value. Research should use benefit–risk frameworks that include symptom intensity, function, patient preference and caregiver impact.[36]

## X. CHALLENGES AND LIMITATIONS

A major limitation is incomplete and uneven biological data. Well-studied proteins tend to have more reported interactions and may dominate centrality analyses, while less characterized cell types or disease subgroups may be underrepresented. Databases can contain inferred associations, duplicate records and findings from non-neural tissues. Researchers should inspect primary evidence, record confidence scores and avoid treating every network edge as equally reliable.[15]

A second limitation is the gap between association and causality. A gene may be associated with disease without being a driver, and a highly connected protein may be essential for normal cellular function. Inhibiting such a node could worsen neuronal viability or systemic health. Directionality, timing and cell-type context are important because inflammatory and stress responses may be protective early and harmful later. Experimental perturbation and longitudinal evidence are needed.[22]

CNS pharmacology presents additional challenges. Many candidate compounds do not achieve adequate unbound concentrations in the brain because of the blood–brain barrier, active efflux, metabolism or limited distribution. Peripheral target engagement may not translate into central effects. Age-related changes, comorbidities, organ impairment and polypharmacy further affect exposure and tolerability and should be integrated early in candidate selection.[19]

The evidence linking network predictions to palliative outcomes remains limited. Many network studies explain disease mechanisms or propose neuroprotective candidates rather than test symptom relief, quality of life or caregiver outcomes. Clinical palliative research also faces challenges in recruitment, disease heterogeneity, communication impairment and outcome selection. Collaboration among computational scientists, pharmacologists, neurologists, palliative specialists, patients and caregivers is needed.[38]

Table 3. Translational barriers and recommended approaches[36]

| Challenge | Why it matters | Recommended approach |
|---|---|---|
| Database bias | Can distort hubs and pathway ranking | Use multiple sources, evidence provenance and sensitivity analyses |
| Association vs causality | May prioritize non-causal or unsafe targets | Use perturbation studies and cell-specific validation |
| BBB and exposure | Predicted target may not be reached in CNS | Measure unbound brain exposure and target engagement |
| Polypharmacy and frailty | Raises interaction and adverse-event risks | Map interactions and test clinically relevant safety |
| Disease/symptom heterogeneity | Average effects may conceal responder groups | Stratify by phenotype, genotype, stage and goals |
| Missing palliative endpoints | Molecular change may not improve lived experience | Measure symptoms, function, QoL and caregiver outcomes |
| Reproducibility | Database and threshold choices alter outputs | Publish versions, code, thresholds and validation data |

## XI. FUTURE PERSPECTIVES

Future work should move from generic disease networks toward context-specific models representing disease stage, cell type, brain region, genotype, comorbidity and symptom phenotype. Multi-omics integration may identify molecular subgroups, while longitudinal sampling can reveal changing network relationships. Such models could support more precise candidate selection and reduce the assumption that a pathway has the same role across all patients or stages.[37]

Artificial intelligence and machine learning may improve prioritization by integrating chemical, biological and clinical datasets, predicting drug–target relationships and identifying candidate combinations. Their usefulness depends on data quality, external validation, interpretability and avoidance of information leakage. Mechanistic network models should complement rather than replace domain expertise and experimental work; predictions should be communicated with uncertainty estimates and evidence grades.[38]

Patient-reported outcomes and caregiver perspectives should be incorporated into computational research design. Clinical phenotypes can be represented as measurable endpoints and mapped to candidate biological processes, while adverse effects and treatment burden are considered alongside predicted benefit. This would make network-guided research more responsive to the priorities of people living with neurodegenerative disorders and their families.[39]

Prospective programmes should use a staged go/no-go framework. Candidates should advance only when target evidence, exposure, safety, reproducibility and a plausible symptom-related mechanism are adequate. Early clinical studies should evaluate feasibility, tolerability and target engagement before efficacy claims are made. Later studies should use validated

symptom and quality-of-life measures and compare the candidate with appropriate standard care.[25,40]

## XII. CONCLUSION

Network pharmacology provides a systems-level framework for exploring the molecular complexity of neurodegenerative disorders and prioritizing multi-target or repurposed candidates. Its relevance to palliative management lies in helping researchers investigate mechanisms associated with symptoms, identify plausible targets and anticipate interactions within biological and medication networks. Computational predictions do not constitute evidence of clinical benefit and cannot replace established multidisciplinary palliative care. Progress requires transparent methods, disease- and symptom-specific network construction, experimental confirmation, CNS exposure assessment, safety evaluation and clinical outcomes reflecting comfort, function, quality of life and caregiver needs. The most productive direction is a patient-centred translational model in which network pharmacology informs, but does not dictate, clinical research and therapeutic decisions.[15]

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