# Pharmacological therapies for early and long-term recovery in disorders of consciousness: Current knowledge and promising avenues

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INTRODUCTION
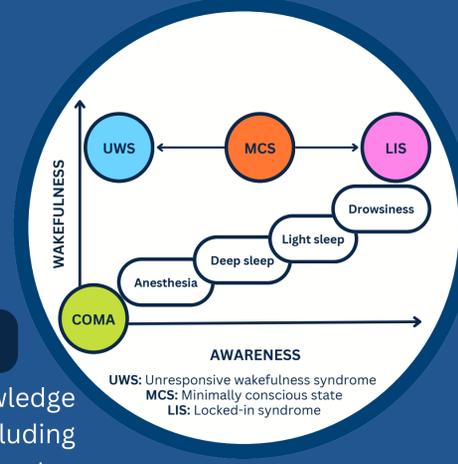
Disorders of Consciousness (DoC)

DOCs are altered consciousness states that can occur after a severe brain injury (traumatic brain injury, stroke, anoxic brain injury, etc.) either in a permanent or transitory manner. They are distinguishable by the level of awareness and arousal of the patient. DOC patients can have varying levels of arousal, but present inconsistent or absent behavioural signs of awareness.

Aims of this expert opinion review

In this perspective, we first aim to summarize the current state of knowledge regarding the effectiveness of key pharmacological interventions, including dopaminergic and GABAergic agents, antidepressants, statins, and anticonvulsants in promoting the recovery of consciousness in DoC patients. Secondly, we propose potential new pharmacological approaches, along with frameworks for future research.

UWS: Unresponsive wakefulness syndrome
MCS: Minimally conscious state
LIS: Locked-in syndrome
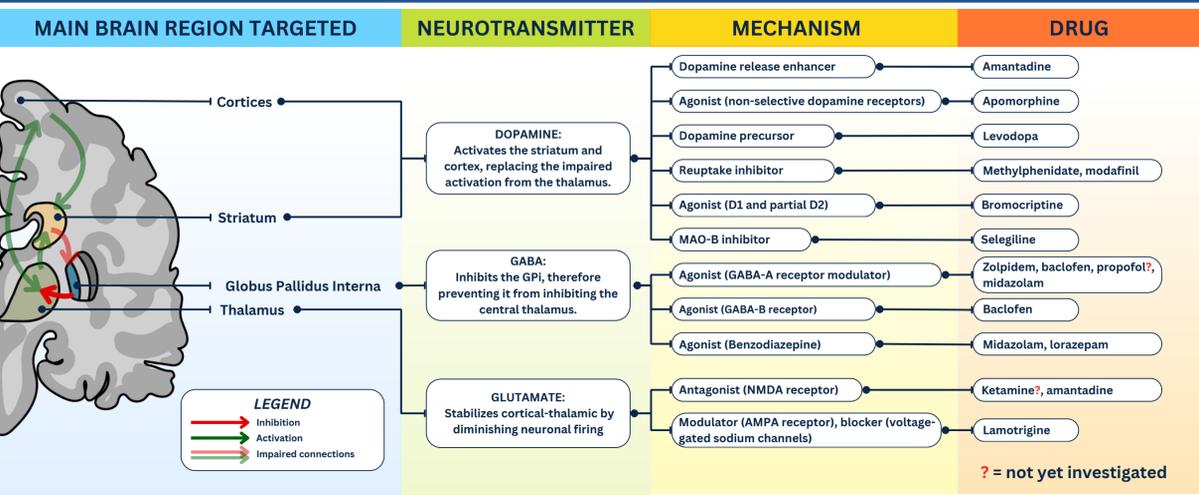
REVIEW

State of the field and level of evidence:

AGENTS INVESTIGATED IN THE LITERATURE:

Dopaminergic agents: Amantadine, levodopa, apomorphine, methylphenidate, modafinil, bromocriptine, selegiline.
Gabaergic agents: Zolpidem, benzodiazepines, baclofen
Other: Antidepressants, statins, anticonvulsants

Amantadine & zolpidem: most studied
Amantadine is the only drugs currently in recommandation guidelines.

CONCLUSIONS

- Various drug classes show potential to improve wakefulness, awareness, and responsiveness in DoC patients.
- Effects remain **variable and modest** across individuals; evidence is still **preliminary**.
- Heterogeneity in injury time, dosage, and patient profiles limits standardization.
- **Mechanisms and therapeutic targets** of these agents in DoC remain largely **unknown**.
- Most treatments are **off-label**, discovered through **trial-and-error**, with few large-scale clinical trials.

MAIN BRAIN REGION TARGETED	NEUROTRANSMITTER	MECHANISM	DRUG
Cortices	DOPAMINE: Activates the striatum and cortex, replacing the impaired activation from the thalamus.	Dopamine release enhancer	Amantadine
Striatum		Agonist (non-selective dopamine receptors)	Apomorphine
		Dopamine precursor	Levodopa
		Reuptake inhibitor	Methylphenidate, modafinil
		Agonist (D1 and partial D2)	Bromocriptine
		MAO-B inhibitor	Selegiline
Globus Pallidus Interna	GABA: Inhibits the GPi, therefore preventing it from inhibiting the central thalamus.	Agonist (GABA-A receptor modulator)	Zolpidem, baclofen, propofol?, midazolam
Thalamus		Agonist (GABA-B receptor)	Baclofen
		Agonist (Benzodiazepine)	Midazolam, lorazepam
	GLUTAMATE: Stabilizes cortical-thalamic by diminishing neuronal firing	Antagonist (NMDA receptor)	Ketamine?, amantadine
		Modulator (AMPA receptor), blocker (voltage-gated sodium channels)	Lamotrigine

LEGEND
→ Inhibition
→ Activation
→ Impaired connections

? = not yet investigated

SUSPECTED PHARMACOLOGICAL TARGETS ACCORDING TO THE MESOCIRCUIT HYPOTHESIS

Example of unifying framework that could be used to understand and predict the response to pharmacological agents in DoC

OPINION

Improving the pharmacotherapy of DoC

Robust clinical trials

Few large RCTs; existing ones are small and single-center, limiting generalizability.

- Multi-center collaboration and a global trial registry are needed to build robust evidence
- Long-term effects and safety of repeated drug use remain unclear.
- **Future focus:** conduct large, longitudinal, multi-center trials and develop stage-specific, personalized treatments.

Redefined outcomes

Current measures emphasize short-term responsiveness, overlooking broader recovery

- Outcome definitions are inconsistent and often limited to behavioral responsiveness.
- New biomarkers and behavioral indicators of consciousness are emerging.
- Subjective scales can help patient and family perspectives more efficiently.

Early intervention

- Early intervention studies, even in the acute phase, are safe, feasible, and may favorise **neuroplasticity.**
- Benefits from earlier pharmacological interventions could outweigh potential risks.

Unified frameworks

Urgent need for biomarkers of consciousness that can inform individualized treatment.

Need for structured frameworks such as:.
- Critical brain hypothesis
- Neural complexity
- Mesocircuit hypothesis

Personalized medicine

Guided by patient-specific neurophysiological and genetic profiles

- Etiology, age, sex, genetics and injury profile undermine a one-size fits-all treatment.

Solution(s):

- AI modeling: could predict drug responses and treatment outcomes.
- Toward adaptive care: real-time brain monitoring enables dynamic interventions

New pharmacological options

Exploration of less conventional pharmacological options

- **Propofol:** may restore neural dynamics or induce paradoxical arousal.
- **Psychedelics** (ketamine, psilocybin): Increase brain complexity; support internal awareness.
- **Saxagliptin** (AI-identified): targets neurotransmission, inflammation and oxidative stress.
- **Combination:** drug + rTMS or rehabilitation may enhance neuroplasticity and recovery

DISCUSSION

HOW CAN WE APPLY SUCH A FRAMEWORK TO A REASEARCH CENTER LIKE OURS?

Cooperating with clinical teams

Collaboration between clinical and research teams can enable data collection without complex protocols

Taking advantage of current practices

Many agents are already used clinically and can be repurposed and evaluated for DoC recovery.

Exchanging between teams

Sharing theoretical frameworks linking brain state to drug responsiveness could strengthen our understanding and pave the way for personalized pharmacotherapy in DoC.

Collaboration with families and patients

Future research should integrate pharmacological treatments with rehabilitation and family education to promote functional and cognitive recovery that truly improves quality of life.

SOURCES: Girard Pepin, R., Seyfzadeh, F., Williamson, D., Gosseries, O., & Duclos, C. (2025). Pharmacological therapies for early and long-term recovery in disorders of consciousness: current knowledge and promising avenues. Expert Review of Neurotherapeutics, 25(6), 613–633. https://doi.org/10.1080/14737175.2025.2500757

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