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PERSPECTIVE

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

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ABSTRACT

Introduction: Disorders of consciousness (DoC) are characterized by impaired arousal and/or awareness, ranging from coma to unresponsive wakefulness syndrome, minimally conscious state, and cognitive motor dissociation. Pharmacological treatment options remain limited, complicated by the heterogeneity of etiologies, such as traumatic brain injury, stroke, and infections. The lack of rigorous clinical trials has led to off-label use of treatments, often without clear mechanistic understanding, posing challenges for effective patient care.

Areas covered: In this perspective, the authors report on key studies concerning the effectiveness of pharmacological interventions, including dopaminergic and GABAergic agents, antidepressants, statins, and anticonvulsants, in promoting recovery of consciousness in DoC.

Expert opinion: Robust longitudinal clinical trials are needed, with priority given to early subacute phase intervention. Outcomes should be better defined, considering immediate responses to medication while also increasing the emphasis on long-term quality of life. Unified functional and mechanistic frameworks are needed to guide research and foster collaboration. Furthermore, a shift toward personalized medicine would benefit this heterogeneous population. Moving forward, assessing the efficacy of more unconventional or 'paradoxical' pharmacological options in treatment plans will be essential. The authors also expect an increased use of AI tools to identify factors that best predict treatment responses.

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Pharmacotherapy; disorders of consciousness; coma; unresponsive wakefulness syndrome; minimally conscious state; criticality; mesocircuit; personalized medicine

1. Introduction

Disorders of consciousness (DoC) are a group of conditions characterized by impaired wakefulness and/or awareness following a severe brain injury. These disorders range from coma, marked by an absence of both awareness and wakefulness, to unresponsive wakefulness syndrome (UWS) (also known as vegetative state (VS)), where patients show wakefulness without behavioral signs of awareness, to the minimally conscious state (MCS), where wakefulness is present with minimal but consistent signs of awareness (e.g. visual pursuit, response to commands) [1]. Further distinctions subdivide MCS into MCS+ and MCS- based on the presence (MCS+) or absence (MCS-) of signs of language processing, such as intelligible verbalization [2]. Additionally, brain activity assessed through active paradigms using electroencephalography (EEG) or functional magnetic resonance imaging (fMRI) can identify cognitive motor dissociation. In this state, there are no observable behavioral signs of awareness, but evidence of preserved cognitive functioning, or covert consciousness, is detected through neuroimaging or electrophysiological assessments [3–5]. Recognizing these distinctions is essential for accurate diagnosis, prognosis, and care management.

The demographics of DoC are diverse, affecting individuals across all age groups with prevalence patterns shaped by factors such as sex and etiology. Additionally, geographic and demographic factors influence incidence rates, which fluctuate between countries due to differences in healthcare systems, injury prevention measures, and reporting practices [6]. This heterogeneity is further explained by the varied causes of DoC, which include but are not limited to traumatic brain injuries (TBI), vascular events (e.g. hemorrhagic or anoxic injuries, stroke), and infections. These causes introduce variability in the type, location, and extent of brain injuries, making it difficult to identify a single mechanism of DoC [7]. Treatment of DoC is also complexified by the vastly different medical conditions and settings in which patients find themselves in acute (0–28 days), subacute (28 days to 3 months for non-TBI DoC; 28 days to 12 months for TBI-induced DoC), and chronic (>3 months for non-TBI DoC; >12 months for TBI-induced DoC) phases post-injury [8]. As a result, a 'one-drug-cures-all'

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Article highlights

- Various pharmacological classes—including dopaminergic and GABAergic agents, antidepressants, statins, and anticonvulsants—have been explored in the treatment of disorders of consciousness (DoC), yet few have demonstrated consistent efficacy.
- The treatment of DoC is hindered by several challenges: heterogeneous etiologies and patient demographics, limited emphasis on long-term quality of life, a lack of structured clinical trials, and insufficient mechanistic understanding of underlying pathologies.
- We propose six key priorities for the development of effective pharmacotherapy in DoC: (1) implementation of robust clinical trials; (2) exploration of early-phase interventions to promote recovery during the window of enhanced neuroplasticity following brain injury; (3) redefinition of outcome measures; (4) unification of research frameworks to enable multicenter collaboration; (5) development of personalized treatment strategies; and (6) identification of novel pharmacological targets, including paradoxical responses aligned with the criticality hypothesis.
- Progress in this field will require a shift toward collaborative, mechanistically informed, and precision-based approaches tailored to the complexity of the DoC population.

approach is impractical, as there is no universal therapeutic target for this complex pathology [9,10].

From this array of etiologies arises a multitude of potential underlying neural and biochemical mechanisms that may explain the loss of consciousness. While much remains unclear, several key pathways have been identified. Structural brain damage is known to disrupt arousal, and different etiologies tend to affect these regions in distinct ways. For instance, hypoxia and ischemia often result in widespread cortical and subcortical damage, frequently impacting the ascending reticular activating system and the thalamus [11]. This system connects the brainstem reticular formation to the thalamus, basal forebrain, hypothalamus, and cerebral cortex, and is considered the primary mediator of arousal [11,12]. The thalamus, through its connections with the striatum and the cortex, plays a critical role in mediating, integrating, and modulating the interactions between brainstem arousal systems and cortical regions responsible for awareness [13]. In addition, extensive cortical damage, particularly affecting the frontoparietal network and the default mode network [14–16], can further impair awareness. In the context of TBI, diffuse axonal injury is common following severe impact. It involves widespread axonal shearing, especially in white matter tracts, which leads to severe network disconnection [17]. Finally, injuries to the motor, visual, or auditory networks may cause impairments that further complicate the clinical evaluation of consciousness levels [3].

Historically, DoC treatments have focused on enhancing wakefulness and/or awareness and neural activity, often using dopaminergic stimulants, without detailed mechanistic insights into DoC pathology [18,19]. However, some hypothesized mechanisms can guide the approach to pharmacotherapy. For instance, the mesocircuit hypothesis suggests that dysfunction within the thalamo-striatal-cortical loop contributes to the loss of consciousness [20,21]. Following injury, the thalamus becomes overly inhibited, preventing it from sending the excitatory afferent signals to the cortex and striatum that are necessary to maintain consciousness [20,21] (Figure 1). A recent investigation of mean fractional amplitude of low frequency fluctuations as a proxy for spontaneous resting-state brain activity in patients with TBI-induced DoC and healthy controls supported mesocircuit assumptions, showing reduced responses in cortical regions representing the default mode network and increased responses in subcortical regions representing the ascending reticular activating system in patients with DoC. These results were indicative of the role of disrupted cortical and thalamocortical connections in the impairment of consciousness. In parallel, exploration of biological underpinnings of DoC through mapping spatial gene expression data using Allen Human Brain Atlas showed that 2080 genes are differentially expressed in brain regions

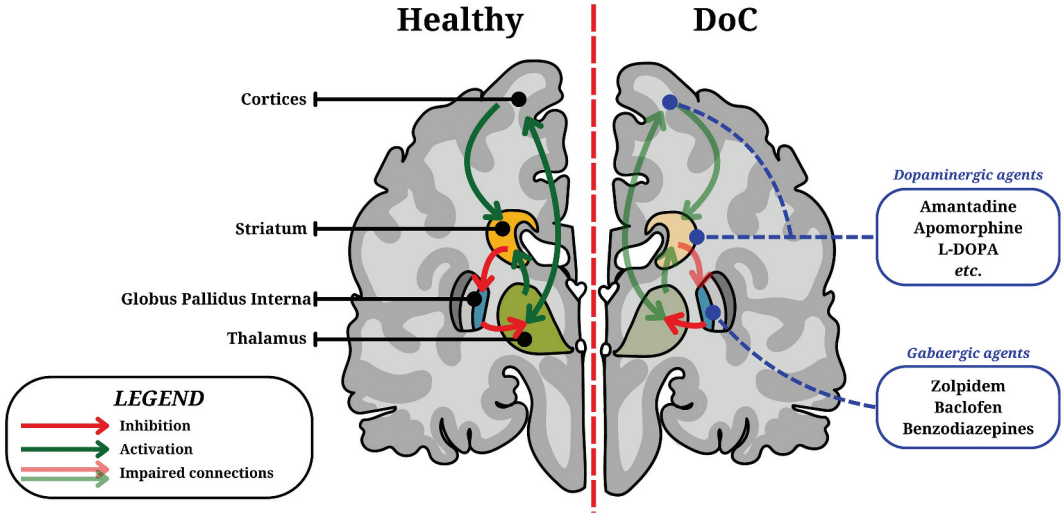

Figure 1. The mesocircuit model in DoC: general pathophysiology and therapeutic mechanisms. The mesocircuit model is a proposed framework to explain the pathophysiology underlying DoC, emphasizing the role of multifocal brain injuries in destabilizing neural circuits, particularly within the frontal/prefrontal cortical–striatopallidal–thalamocortical loop. Loss of striatal inhibition on the globus pallidus interna (GPi) leads to excessive thalamic inhibition, disrupting its ability to send excitatory signals to the striatum and cortical regions. These disruptions, also observed in states like sleep and anesthesia, are thought to contribute to consciousness impairment in DoC. The model identifies potential pharmacological targets, although its clinical assessment remains challenging.

with reduced activity in patients with DoC, portraying impaired synaptic function, oxytocin signaling, and GABAergic transmission (excitatory/inhibitory balance) [22]. However, such hypotheses remain underexplored in robustly designed interventional contexts, with limited translation between theoretical models, research, and clinical practice. The biological mechanisms of DoC are still misunderstood, and clear biomarkers to guide therapy are yet to be identified. Most pharmacological approaches to treating DoC rely on the off-label use of drugs, often applied on a trial-and-error basis and, in most cases, studied without rigorous prospective clinical trials. This highlights the urgent need for personalized medicine that considers variability in etiology, clinical presentation, and patient characteristics to optimize outcomes.

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. We also discuss why, in our view, the future of DoC research will be propelled by (1) conducting larger, more comprehensive, and longitudinal randomized controlled trials (RCTs); (2) implementing earlier pharmacological interventions; and (3) redefining what constitutes a successful outcome. Grounding these changes in unified theoretical frameworks is essential, as it will help advance the goal of developing more personalized approaches and exploring new pharmacological avenues to enhance recovery in DoC.

2. Dopaminergic agents

Dopaminergic agents enhance cognitive function in healthy individuals [23] and are widely used to manage neurological conditions like Parkinson's disease. In DoC, they are among the most utilized drug classes. Their therapeutic effects likely stem from enhancing dopamine transmission within the striato-thalamo-cortical loop, compensating for reduced activation normally provided by the thalamus [24]. Amantadine, levodopa, apomorphine, methylphenidate, modafinil, and bromocriptine, each targeting distinct aspects of dopaminergic transmission, have been studied for their efficacy in this population.

2.1. Amantadine

Amantadine, an N-methyl-D-aspartate (NMDA) receptor antagonist, is approved by the U.S. Food and Drug Administration (FDA) to alleviate tremor, rigidity, and medication-induced dyskinesia in Parkinson's disease [25,26]. With the dysregulation of dopaminergic pathways particularly in the frontal cortex, striatum, cerebellum, and hippocampus following a TBI [27], amantadine was considered as a potentially effective therapeutic agent as its neuroprotective effects can promote functional recovery in some patients with DoC through downregulation of dopamine reuptake and upregulation of dopamine receptor density [24]. Based on the current practice guideline in DoC published by the American Academy of Neurology in 2018, amantadine is the only recommended pharmacotherapy for adult patients with TBI-induced DoC in subacute phases [28].

In the 1990s, case reports on one UWS (TBI, three years post-injury) and one MCS (non-TBI, 5 months post-injury) patients indicated that amantadine might aid in the recovery of consciousness in DoC [29,30]. In both reports, amantadine was initially administered in increasing doses, with the optimal response observed at the maximum dosages (300 mg and 400 mg daily, respectively). This was followed by a withdrawal period during which the improvements disappeared. However, the reports differed in the effects of long-term administration: in the patient with UWS, the effects tapered off with repeated use, whereas in the other case, the improvements persisted and ultimately allowed for the drug to be discontinued without loss of benefit [29,30]. These reports were later supported by more robust placebo-controlled RCTs in TBI patients, spanning various stages post-injury: from the acute phase (a few days post-injury [31]), to the (sub)acute phase (up to 6 weeks [32]) and subacute/prolonged phase (4 to 16 months [33]).

The positive effects of amantadine on the level of consciousness have been observed in subacute and chronic DoC with TBI [33,34] and non-TBI [35–38] etiologies. A fixed-effects meta-analysis of two placebo-controlled RCTs, along with a sensitivity analysis of a third placebo-controlled RCT, assessed the effects of repeated amantadine administration (4–6 weeks) in 281 adult patients with TBI-induced DoC. The findings demonstrated potential benefits, with functional improvements observed in weekly Disability Rating Scale (DRS) scores during the intervention period and at the 6-month follow-up. However, given the significant heterogeneity across the studies, the more appropriate random effects analysis revealed no significant difference between amantadine and placebo [39].

Despite being the most studied pharmacological intervention for promoting recovery from DoC, the beneficial effects of amantadine are not consistently observed across studies, likely due to methodological limitations such as suboptimal study designs, inadequate assessment measures, and small sample sizes. For instance, a retrospective study comparing the effects of amantadine, modafinil, and standard care in an (sub)acute context (median medication initiation at 13 days post-injury) found that TBI-induced DoC patients receiving standard care demonstrated higher Glasgow Coma Scale (GCS) scores and shorter hospital stays. In this study, amantadine and modafinil were administered once daily over a median duration of 14 days [40].

With most of the previous studies focusing on TBI etiologies, evidence supporting its efficacy in non-TBI cases remains scarce. Most recently, a double-blind, placebo-controlled study in 37 adult patients with subacute non-TBI DoC (aneurysmal subarachnoid hemorrhages) found no consciousness improvement on the Coma Recovery Scale-Revised (CRS-R) after the 6-week amantadine administration and no functional improvements on the modified Rankin Scale (MRS) or the Glasgow Outcome Scale (GOS) at the 3- and 6-month follow-up [41]. However, these findings may be limited by the small sample

size. Mainly recommended for use in adult patients with DoC, amantadine was also investigated in five pediatric patients (3 TBI) in a small placebo-controlled crossover pilot RCT. Although patients receiving amantadine did not show improvements on the Coma/Near-Coma Scale (CNCS) or CRS-R, physicians subjectively reported behavioral improvements during the 3-week amantadine administration period, compared to placebo [42].

Overall, while amantadine shows potential consciousness-enhancing effects in TBI-induced DoC, its suitability for other etiologies, recovery phases, and patient populations remains uncertain. It should also be noted that some patients experienced adverse reactions, including seizures, paralytic ileus, and tachycardia [41].

2.2. Levodopa

Levodopa (L-Dopa) is a large neutral amino acid precursor to dopamine, norepinephrine, and epinephrine [43]. When prescribed, levodopa must be combined with a decarboxylase inhibitor, like carbidopa or benserazide, to prevent its breakdown. Levodopa combinations are FDA-approved for treating Parkinson's disease and motor fluctuations in its advanced stages [44]. The rationale for its use in DoC is based on its potential to benefit patients with brain injuries that selectively disrupt dopaminergic pathways, particularly in cases involving damage to the brainstem, where such systems are primarily located [45]. So far, several case reports and case series documented positive changes in patients' clinical conditions and diagnoses following levodopa administration [45–47] in patients with TBI-induced DoC [45,46,48–50].

These case studies documented command-following [45,46,51], reduced muscular rigidity and akinesia [45,49], reduced involuntary movements, improved sound localization, assisted walking and later ambulation, visual pursuit, and verbalization and communication [45,46]. In a case-series of 11 patients (one pediatric) in chronic UWS, levodopa/carbidopa twice daily (initiation at 100/25 mg twice daily and augmented until reaching 300/75 mg daily) resulted in overall improvements (i.e. command-following, communication, ambulation) in nine (82%) patients and significant improvements in four (36%), with the other two showing no improvements [47]. Clinical improvements (e.g. eye opening, improved hand movement, increased strength, verbalization, and non-verbal communication) were observed for more than 6 months of daily levodopa administration (100/25 mg thrice daily) in an MCS patient three weeks post-injury with a non-TBI etiology (aneurysm rupture) and no extrapyramidal signs. However, dose reduction led to a regression in recovered communication skills, which improved again upon re-administration of the initial dose [52].

According to the existing evidence, highly prevalent motor impairments in DoC can be well-targeted using levodopa. Yet, most previous studies on levodopa have focused on TBI-induced DoC. Therefore, there is little evidence as to its efficacy in non-TBI population. Additionally, the mechanisms remain underexplored, and no specific patient profiles have been identified.

2.3. Apomorphine

Apomorphine is a potent direct agonist of dopamine with an affinity for D1 and D2 receptors, approved by the FDA to address hypomobility associated with advanced Parkinson's disease [53]. The rationale for investigating apomorphine in DoC aligns with that of levodopa, hypothesizing that it may help restore disrupted dopaminergic transmission following severe brain injury, potentially leading to behavioral signs of consciousness recovery and associated neurophysiological improvements [54–56].

In a single-patient case study, a patient in MCS following a TBI demonstrated command-following and communication on the first day of a six-month, 12-hour daily infusion of apomorphine using a dose escalation infusion rate from 2 mg/h to 8 mg/h during the subacute and chronic phases starting at day 104 post-injury, ultimately achieving full recovery and extensive functional improvements [54]. A later study following the same protocol also documented full consciousness recovery in seven out of eight (88%) patients with subacute (1–4 months post-injury) TBI-induced UWS and MCS, with the effects maintained over a 1-year follow-up [55]. In a recent multimodal open-label study, six DoC patients (UWS and MCS) with mixed etiologies received a daily 12-hour infusion of apomorphine for 30 days during the subacute and chronic phases (63–146 days post-injury). The results showed a positive diagnostic change in four out of six (67%) patients at the 6- and 12-month follow-up, compared to one out of seven (14%) in the standard-of-care control group. Additionally, the apomorphine group showed increased alpha-band whole-brain connectivity, improved temporo-parietal connectivity, and higher whole-brain metabolism after one month of treatment [56].

The limited but promising evidence thus far supports further research into apomorphine as a potential treatment for DoC. Ongoing placebo-controlled RCTs may provide valuable insights into its effectiveness in acute, subacute, and chronic phases of DoC [57,58].

2.4. Methylphenidate

Methylphenidate stimulates dopamine and norepinephrine release and inhibits reuptake of these catecholamines, regulating arousal and reward systems through dorsal and ventral pathways in the central nervous system [59]. This drug is approved by the FDA for the treatment of attention deficit disorders and narcolepsy [60,61]. It has also been explored for cognitive enhancement in epilepsy [62]. Given its stimulant effects, methylphenidate is a logical, yet understudied, option for investigation in the context of DoC pharmacology. This medication also offers significant advantages, with a short half-life (~2 hours), rapid peak effect (~1 hour), and minimal side effects [63,64].

In 1999, a placebo-controlled single-case study of a patient in prolonged DoC following a severe TBI examined the effects of bi-daily methylphenidate administrations over four weeks on verbal command-following and visual stimulus identification, finding significant improvement in the former compared to placebo [63]. Later, a meta-analysis of single-case trials

involving a median dose of 10 mg of methylphenidate, generally administered twice daily to 22 patients with chronic DoC (17 TBI), found no significant drug effect in terms of command-following and communication [65]. A double-blind placebo-controlled cross-over study in 62 acute patients with TBI-induced DoC showed that patients receiving daily methylphenidate (0.3 mg/kg up to 20 mg per day) had significantly higher GOS scores at hospital discharge and shorter Intensive Care Unit (ICU) and hospital stays. However, no significant differences were found between the active and the placebo groups in terms of GCS scores, mortality rate, or delirium (Confusion Assessment Method for the intensive care unit (CAM-ICU)) [66]. In pediatric patients, a case series reported the beneficial effects of methylphenidate, including its sustained efficacy during continued daily administration in a child with acute cognitive motor dissociation following a TBI [67].

Though several studies have shown that methylphenidate could improve attention, mental fatigue, and other cognitive functions [68], evidence supporting its use in DoC specifically remains sparse and focuses primarily on TBI patients. The Connectome-based Clinical Trial Platform was proposed to investigate methylphenidate's role in TBI-induced acute DoC recovery by targeting dopaminergic circuits in the ascending arousal network [69]. While it considers adverse events and resting-state MRI and EEG as outcomes, findings from its application are yet to be reported.

2.5. Modafinil

Modafinil is a wakefulness-promoting pharmacological agent, which binds to the dopamine transporter and inhibits dopamine reuptake, leading to increased arousal and alertness [70]. It is commonly prescribed for excessive daytime hypersomnolence in sleep disorders (i.e. narcolepsy, apnea/hypopnea) [71]. Its potential to enhance wakefulness and possibly awareness has also been explored in patients with DoC [40,72,73].

A retrospective study of 24 patients with chronic DoC due to mixed etiologies showed that a four-week modafinil administration with dose escalation significantly promoted cognitive recovery as documented by the Wessex Head Injury Matrix (WHIM) as well as consciousness recovery in 11 out of 24 (46%) patients (7 TBI), showing a favorable change of diagnosis (CRS-R) [72]. A retrospective observational study evaluated repeated administration of 100 to 200 mg of oral modafinil in 13 patients over six to 24 days, comparing its effects to amantadine and standard care in patients with TBI-induced acute DoC. Modafinil was found more effective based on the improvement of GCS scores [40].

In the only case report on an 'unresponsive' pediatric DoC patient with 'insufficient wakefulness' (CNCS score of 0, LOCFAS level 3) from a non-TBI etiology (pilocytic astrocytoma), modafinil (100 mg twice daily) combined with nightly melatonin (1 mg daily) and rehabilitation improved circadian rhythms and increased daytime wakefulness. This followed limited success with fluoxetine, which had caused irritability and agitation. Clinical and 24-hour polysomnographic assessments indicated restored circadian rhythm, improved wakefulness, appropriate emotional expression, object recognition, higher CNCS and DRS scores, and partial restoration of circadian rhythms [73]. As with the other dopaminergic agents mentioned so far, the limited evidence and lack of RCTs leave its effectiveness in DoC inconclusive, highlighting the need for further investigation.

2.6. Bromocriptine

Bromocriptine is a dopamine D2 receptor agonist, which activates postsynaptic dopamine receptors [74]. It is indicated by the FDA for the treatment of hyperprolactinemia-associated dysfunctions [75]. The benefits of bromocriptine in Parkinson's treatment are attributed to its stimulation of dopamine receptors in the striatum, a pharmacological target also implicated in the treatment of DoC, as suggested by the mesocircuit hypothesis (Figure 1) [13].

An early study on five ≥ 16-year-old patients with TBI-induced acute UWS indicated that repeated daily administration of bromocriptine (initial dose of 1.25 mg twice daily, augmented to 2.5 mg twice daily) for 2–6 months along with sensory stimulations as well as physical, occupational, and speech therapy improved from UWS to MCS, as well as improved functional outcomes as documented by CRS-R, DRS, and Functional Independence Measure (FIM™) at 1-, 3-, 6-, and 12-month follow-up assessments [76]. Bromocriptine was also investigated in an uncontrolled observational study on 33 adults and three pediatric patients with TBI-induced chronic MCS (pediatric dose: 3.75 mg daily; adult dose: 7.5 mg daily). Over a follow-up period of 1 to 6 months, outcomes assessed included level of consciousness (GCS), aphasia, speech fluency, cognitive function, and functional independence. Overall, arousal increased in eight out of 17 patients (47%), GOS scores improved in seven out of 17 patients (41%) within 3 months, hemiparesis improved in five out of nine patients (56%), aphasia improved in four out of five patients (80%), and cognitive function and memory improved in three out of five patients (60%) [77]. An uncontrolled retrospective case series showed that a > 1-month bromocriptine administration (from 2.5 mg twice daily to up to 7.5 or 12.5 mg twice daily) in ten patients with TBI-induced DoC led to eight (80%) patients having a higher score at the time of discharge. Two other patients progressed from UWS to MCS [78].

So far, beneficial effects of bromocriptine have been noted only in chronic TBI-induced DoC, with no significant adverse reactions reported. However, due to the low-quality evidence (mainly uncontrolled studies), it is possible that observed improvements may, in part, also be due to spontaneous recovery.

2.7. Selegiline

Selegiline is a selective monoamine oxidase type B (MAOB) inhibitor, which acts on fronto-striatal dopaminergic circuits [79]. This FDA-approved pharmaceutical is used as a treatment for major depressive disorder and as an adjunct treatment for Parkinson's disease [80]. Its effects on the improvement of apathy and cognitive performance [79] have led to its investigation as a potential treatment for DoC.

An only off-label daily administration of selegiline through percutaneous gastrostomy in ten subacute and chronic UWS, MCS, and eMCS patients with mixed etiologies in an open-label pilot study improved the level of consciousness in four (40%) and increased arousal levels in three (30%) patients, as documented by weekly CRS-R assessments during a 10-week treatment (5 mg daily for one week, augmented to 10 mg daily afterward) [79]. Considering treatment discontinuation in three out of ten (30%) patients due to adverse reactions (protracted diarrhea, persistent supraventricular tachycardia), the open-label design, the small sample size, the absence of a control group, and mixed etiologies in the single study on selegiline [81], it is too early to formulate recommendations for its use in DoC patients.

3. GABAergic agents

GABAergic agents, primarily agonists, are commonly used as sedatives for the treatment of insomnia and anxiety. However, in brain-injured patients, they can produce paradoxical effects. They are hypothesized to promote the recovery of consciousness in DoC by interacting with GABA receptors within the mesocircuit [20]. Specifically, these agents may inhibit the globus pallidus interna, which in turn reduces its inhibition of the thalamus [21]. The thalamus can then activate, restoring activity to the cortices and other brain regions, ultimately resulting in awareness (Figure 1) [24,82]. Currently, most research focuses on zolpidem and baclofen, with newer studies exploring benzodiazepines such as midazolam and lorazepam.

3.1. Zolpidem

First approved by the FDA as a treatment for insomnia, zolpidem is a modulator of GABA-A receptors, which are found in high density in the globus pallidus interna [53]. Before 2000, it was used within its prescribed indications as a sedative to address restlessness in DoC patients [83].

However, zolpidem (10 mg) was administered to a reportedly 'semi-comatose' TBI patient, unexpectedly leading to significant agitation and remarkable behavioral improvements. These changes were also detectable through single-photon emission computed tomography [84]. Since then, over 25 publications have described its paradoxical effects in DoC. While a few RCTs and thorough studies have been conducted [85–90], many of these reports remain case studies [91–96]. In studies involving larger cohorts, the paradoxical response has been estimated to occur in approximately 5% of DoC patients [85,88,97]. However, it is important to note that the definition of a 'responder' varies significantly across and within studies, ranging from improvements on behavioral scales or change in diagnosis to changes in EEG patterns [85,88,90,98,99]. Although studies so far are promising, it remains premature to draw definitive conclusions.

Most studies on zolpidem have focused on chronic DoC populations, leaving limited evidence regarding its efficacy in acute contexts. Patients in the acute phase are often heavily sedated and medicated, complicating efforts to isolate and interpret the specific effects of the drug. Moreover, clinicians may not readily consider the use of zolpidem during the acute phase of injury as its paradoxical effects are not well-known in early clinical settings. Nevertheless, one case report described a 75-year-old male who lost the ability to respond to commands and perform eye tracking two days after an elective pelvis surgery, which caused postoperative intracranial hypotension-associated venous congestion. Zolpidem (2.5 mg) was administered immediately after this loss of function, and improvements in functionality were observed starting 12 hours later [94]. Intriguingly, given the short half-life of zolpidem (~2–3.5 hours) in healthy adults [100], the delayed behavioral improvements cannot be directly attributed to the drug's immediate effects, warranting further investigation.

In the chronic DoC population, although the use of zolpidem remains off-label, no significant risks or side effects have been reported. Some argue that zolpidem should at least be attempted when no other therapeutic options are effective [89], but several concerns persist. First, it is unclear whether early administration leads to better outcomes. A case study reported the complete functional recovery of a 44-year-old female patient in an MCS following a subarachnoid hemorrhage [93]. A daily dose of zolpidem (10 mg) at week 13 of hospitalization, specifically to enhance arousal and consciousness, was administered once a week over 8 weeks in conjunction with a multidisciplinary intervention program. The patient showed significant improvements in communication and motor function during the anticipated window of zolpidem's effects based on its half-life. However, when zolpidem was combined with the personalized intervention program, these gains were sustained beyond the immediate effects of the drug. This intervention program aimed at preventing sensory deprivation through structured sensory stimulation [93,101]. The sensory input was customized to the patient based on information provided by the family, including the patient's likes, dislikes, interests, roles, and activities before the injury. This study is particularly interesting because the authors hypothesized that earlier intervention could promote neuroplasticity. It also suggests that zolpidem may be more effective in promoting the recovery of awareness when combined with other therapeutic interventions as part of a comprehensive program [93].

The second concern regarding zolpidem is that the efficacy of prolonged administration in responders remains uncertain and appears to depend on the individual case. As reported in a case report of two patients in MCS following TBI, some patients are successfully weaned off zolpidem after a few weeks without losing improvements in consciousness [95]. Others remain on treatment for extended periods, such as one ex-coma TBI patient who continued for two years without issues [102]. In contrast, another patient with akinetic mutism following severe hypoxic-ischemic brain injury reported drug tolerance, where zolpidem lost effectiveness over time [103]. This patient began treatment eight years post-injury, again suggesting that earlier intervention might be more favorable [103].

Finally, studies on zolpidem have been conducted in both TBI [84,90,95,98], non-TBI [91–94,96] and mixed etiologies [85–89,97,99], but no clear distinction has been made regarding

whether the response to treatment is more favorable in one group over the other. A study on 165 patients with mixed etiologies suggests that patients should be classified based on the area of brain damage and injury mechanism rather than broad diagnostic categories. From this, the authors concluded that zolpidem appears to be more effective in individuals with injuries outside the brainstem. Additionally, among responders, the improvement is typically sudden rather than gradual.

3.2. Baclofen

Baclofen, a structural analog of GABA, binds selectively to GABA-B receptors, primarily exerting its effects by inhibiting synaptic reflexes. This inhibition reduces hypertonia and spasticity, making baclofen a key treatment for spasticity and dysautonomia, particularly in patients with DoC [104,105]. Its efficacy in reducing these secondary symptoms has made it a staple in neurorehabilitation. These improvements in spasticity and dysautonomia are often accompanied by secondary enhancements in consciousness, sparking interest in its potential as a consciousness restoration agent. In the context of the mesocircuit hypothesis, baclofen's effects may extend beyond the treatment of spasticity and dysautonomia. When baclofen reaches the cortex, it could positively influence cortico-thalamocortical connections by modulating GABAergic neurotransmission (Figure 1) [106–108]. This modulation may help restore crucial functional connectivity between the thalamus and the cortex.

There are few studies on the use of baclofen in DoC, with most focusing on symptoms related to dysautonomia and spasticity. However, some insights can be drawn from the current literature. Firstly, intrathecal baclofen appears to be more effective in patients with TBI, as highlighted by a 2012 comparative study [109]. Secondly, an observational study reported that the effects on cognitive recovery seem to be independent of its effects on spasticity and dysautonomia [108]. Thirdly, a recent review article notes that the impact on consciousness may take longer to manifest than expected, often emerging well after the typical recovery period based on etiology [104], underscoring the need for more longitudinal studies.

Baclofen may be more suited for the chronic DoC population, as no evidence to date suggests that the oral form improves consciousness, whereas intrathecal delivery has shown potential benefits [107]. However, this method requires a trial injection and a surgical procedure for pump implantation and may lead to withdrawal symptoms when stopped [110]. All these factors may pose significant risks for medically unstable patients in acute settings who are already heavily monitored and subject to more urgent surgeries to treat their acute injuries. Additionally, any effects on consciousness, if present, often take time to manifest, making baclofen less suitable for short-term use. This is especially true given the complexity of its administration and the risk of withdrawal when discontinuing the medication or if the pump runs out [110].

3.3. Benzodiazepines

Benzodiazepines are sedative agents commonly prescribed for a wide range of conditions, including anxiety and insomnia management [111]. Some of the most common benzodiazepines include lorazepam, diazepam, alprazolam, clonazepam and midazolam. Benzodiazepines act as positive allosteric modulators of GABA-A receptors, enhancing the brain's response to GABA [112]. However, in healthy patient populations, benzodiazepines are known to have paradoxical effects on some individuals (agitation, excitation, aggressivity) [113]. This paradoxical response raises the possibility that benzodiazepines could have similar effects in patients with DoC due to the restoration of activity within the thalamocortical loop (Figure 1). It has also been hypothesized that improvements could be related to the drug's effects on catatonia. To our knowledge, only two studies have reported the therapeutic effects of benzodiazepines in DoC patients: one case report on midazolam and one open-label study where 43 patients received lorazepam [89,114].

The first report of paradoxical effects of benzodiazepines was in 2014 on a 43-year-old male in post-traumatic MCS, who began to unexpectedly interact with his family and medical team after receiving midazolam (5 mg in 100 cc of saline solution) in preparation for a computed tomography scan [114]. Remarkably, he was able to hold a conversation, and this state lasted for approximately two hours, concurring with midazolam's half-life of approximately one hour [115]. When midazolam was re-administered a couple of weeks later, the same behavioral changes were observed. These episodes of significant behavioral improvement were correlated with EEG markers of consciousness, specifically an increase in higher frequency activity (14–30 hz) and a reduction in slower activity (1–12 hz) [114].

The first (and only) comparative open-label study on the use of benzodiazepines and zolpidem in DoC patients identified six responders out of 43 participants (14%) receiving lorazepam. These responders demonstrated significant functional improvements such as clear verbalization, enhanced cognitive abilities, and increased engagement with their surroundings. While these improvements required continued administration of the medication, most patients were gradually weaned off benzodiazepines after achieving a certain level of functionality. These findings indicate that benzodiazepines could have a meaningful impact on consciousness recovery in a proportion of DoC patients, beyond anecdotal observations [89]. When comparing the effects of zolpidem and lorazepam, it was concluded that their efficacy in restoring consciousness seems to differ based on etiology (anoxic vs. traumatic). Lorazepam appears to show greater effectiveness in cases of anoxic brain injury [89].

Since both studies on benzodiazepines have focused solely on chronic DoC, further research is needed to specifically explore their potential applications in acute scenarios as well as larger samples of chronic populations.

4. Other pharmacological agents

4.1. Antidepressants

Antidepressants, commonly used in the treatment of mood and cognitive disorders, have also been explored for the pharmacotherapy of DoC. Amongst the most prescribed

antidepressants, selective serotonin reuptake inhibitors (SSRIs) (e.g. sertraline, fluoxetine, fluvoxamine, escitalopram) block serotonin reuptake into presynaptic neurons. SSRIs are usually prescribed for depressive disorders, obsessive-compulsive disorder, bulimia nervosa, and panic disorders [116,117]. Even though SSRIs have shown limited potential in DoC [73], they have been more extensively studied in the context of post-TBI neurocognitive and neuropsychiatric disorders [118].

Another class of antidepressants, however, has been the subject of more comprehensive research. Tricyclic antidepressants (TCAs) (e.g. amitriptyline, desipramine, protriptyline, imipramine) block the reuptake of norepinephrine and serotonin in the presynaptic terminals and are indicated for alleviating depressive symptoms [119,120] and managing neuropathic pain [121]. Given their potential positive impact on cognitive recovery (e.g. attention, memory), the use of antidepressants in the pharmacotherapy of DoC was briefly investigated in two studies [122,123].

An initial case series of eight patients with DoC, emerging from mixed etiologies, showed favorable effects of protriptyline in increasing arousal and promoting initiation, following previous unsuccessful or minimally successful attempts with other agents (e.g. levodopa/carbidopa, methylphenidate, bromocriptine). Importantly, it was discontinued in one patient due to restlessness and irritability despite initial improvements [122]. Another case series involving amitriptyline in one adult patient and desipramine in two others with TBI-induced DoC showed beneficial effects [123]. After an unsuccessful attempt with levodopa/carbidopa to address hypo-arousal, amitriptyline resulted in improvements in arousal, verbalization, functional communication, command-following, assisted ambulation, and eating. Desipramine also enhanced responsiveness, command-following, and assisted ambulation in a patient in the subacute phase, allowing for discharge home. Another patient in the chronic phase showed improvements in simple command-following and verbalizations, leading to discharge to a nursing home [123].

The two studies on tricyclic antidepressants are limited to case reports in uncontrolled conditions; therefore, to draw valid conclusions and ensure the benefits of these agents in the treatment of DoC, more studies with rigorous designs are required. Potential side effects, including anticholinergic and seizure-related reactions [122,123], should also be considered. Although recommended in both studies for nearly 30 years, the research initiative for a more comprehensive understanding of these agents' role in the recovery of consciousness is yet to be undertaken.

4.2. Statins

In healthy individuals, statins are used to reduce low-density lipoprotein cholesterol levels and are indicated for the prevention of cardiovascular and cerebrovascular diseases [124,125]. Due to the pleiotropic neuroprotective and anti-inflammatory characteristics of statins, they have been investigated in the context of brain injury and DoC [126–129].

In a placebo-controlled RCT on 43 acute TBI-induced DoC patients, repeated daily doses of simvastatin (80 mg on the first day followed by 40 mg daily) improved mean GCS scores at discharge but did not significantly affect mechanical ventilation duration, ICU mortality, or ICU stay length [126]. Another placebo-controlled RCT in 98 patients with TBI-induced DoC showed that simvastatin 40 mg daily improved the mean GCS score at discharge and 1-month follow-up compared to the placebo group. There was a significantly higher percentage of conscious patients at the 1-month follow-up in the intervention group (65%) versus the placebo group (28%). No significant differences were reported in the number of conscious patients at discharge, duration of mechanical ventilation, or ICU/neurosurgery length of stay [127].

Overall, the small body of evidence shows that statins can have consciousness-enhancing effects, particularly following a TBI [129]. However, due to the limited scope of studies and the heterogeneity in assessment techniques and patient profiles, the effectiveness of these agents and the optimal phase for their administration remain unclear, necessitating further studies with a more focused emphasis on DoC.

4.3. Anticonvulsants

Anticonvulsants are a class of medications primarily used to prevent and control epileptic seizures by stabilizing neuronal activity and reducing excessive excitability in the brain. Beyond epilepsy, they are also prescribed for conditions such as neuropathic pain, mood disorders (e.g. bipolar disorder), and migraine prevention due to their ability to modulate neurotransmitter function and neuronal firing patterns. Anticonvulsants, particularly lamotrigine, have emerged as a potential treatment for DoC due to their neuroprotective properties and effects on cortical excitability [121,130,131].

A recent international survey on the management of epileptic seizures in DoC highlights the widespread use of anticonvulsants in clinical practice, despite limited consensus on their optimal role beyond seizure control [132]. Given that seizures and abnormal cortical excitability are common in DoC, anticonvulsants may help by stabilizing neuronal activity, preventing excitotoxicity, and potentially facilitating cognitive recovery. However, their effects on consciousness recovery remain underexplored in large-scale studies.

A few case reports and small case series provide preliminary evidence supporting the therapeutic potential of lamotrigine in DoC. A first case series of 13 brain-injured patients (mixed etiologies, 6 TBI) with a Rancho Los Amigos Cognitive Scale (RLACS) score of I-III (behavioral equivalent to DoC) explored the effect of lamotrigine (mean dose of 87.5 mg daily) administration in a rehabilitation setting, initiated in the subacute phase of injury [133]. They reported that 75% of patients progressed 'further than expected' and were surprisingly discharged to the community, which represented a better outcome than typically seen in such a unit, as per the medical personnel's experience. Similarly, another case report of a TBI patient in MCS (RLACS score of III) documented beneficial cognitive effects of lamotrigine initiated in the

subacute phase, resulting in rapid improvement in arousal, cognition, and verbal communication [134]. A recent series of four cases involving severe subacute TBI patients in DoC also found that lamotrigine administration (starting at 25 mg daily, titrated to 200 mg twice daily), following a standard protocol of progressively increasing doses, was associated with behavioral and cognitive improvements and globally improved consciousness [135]. The mechanism of action is thought to involve the stabilization of glutamatergic transmission, reduction of excessive neuronal firing, and enhancement of thalamocortical connectivity [135].

Despite these promising findings, the use of lamotrigine and other anticonvulsants in DoC requires further rigorous investigation. The heterogeneity of DoC populations and methodological limitations complicate the assessment of treatment efficacy. Additionally, while anticonvulsants may help regulate cortical excitability, their potential sedative effects and interactions with other medications must be carefully considered.

5. Conclusion

This review provided a comprehensive summary of pharmacological interventions for the treatment of DoC. Previous studies and cases have indicated the potential of various pharmacological agents, such as dopaminergic and GABAergic drugs, anticonvulsants, and antidepressants, in promoting some degree of recovery in DoC patients, particularly in improving wakefulness, signs of awareness, cognitive functioning, and behavioral responsiveness. Though these findings highlight the untapped therapeutic potential of these agents, their effects remain variable and often modest across different patient profiles, and the overall evidence for many of these interventions remains preliminary. Additionally, the time since injury and drug dosage vary significantly across studies, which further complicates the incorporation of specific drug treatments into standardized clinical guidelines. What is more, the therapeutic targets and mechanisms of these agents, specifically when it comes to the treatment of DoC, are largely unknown. Finally, treatment effectiveness is also constrained by the reliance on off-label use, the at-times fortuitous identification of therapeutic effects, and the lack of rigorous, large-scale clinical trials, especially in the acute setting.

While existing studies lay the groundwork for the use of these drugs in treating DoC, larger, more comprehensive studies are required to confirm their efficacy and determine the best treatment regimens. The variability in patient characteristics, injury etiology, and clinical presentation underscores the necessity of future research with personalized treatment strategies. The next section will propose novel pharmacological strategies, alongside recommendations for future research that could refine and strengthen treatment protocols.

6. Expert opinion

While research on neurotherapeutic interventions for DoC is expanding, significant literature gaps remain. We believe that to progress to the next era of DoC treatment, several key changes must take place. First, the current state of research highlights the need for more robust clinical trials to establish strong evidence and guide future treatment protocols. Importantly, these trials should not be limited to the chronic DoC population alone; earlier intervention also warrants attention. We must also rethink what constitutes a 'good outcome,' shifting focus from immediate effects to the long-term quality of life for individuals with DoC. To attain this goal, personalized medicine interventions are crucial, with pharmacotherapy tailored to individual patient characteristics. However, these personalized approaches cannot be implemented without solid frameworks that promote unification and collaboration across research teams and facilitate multicenter clinical trials. Finally, it is essential to explore new pharmacological avenues to expand the treatment options available for patients with DoC (Figure 2).

Figure 2. Key aspects necessary to the development and improvement of pharmacotherapy for disorders of consciousness (DoC). Central to the future of DoC pharmacotherapy are the implementation of longitudinal randomized controlled trials (RCTs), the consideration of earlier pharmacological interventions, and a redefinition of treatment success in patients with DoC. These efforts should be grounded in unified frameworks to ensure more targeted, effective interventions, ultimately improving outcomes and promoting a more personalized approach to DoC recovery.

6.1. Robust clinical trials

Pharmacotherapy for DoC predominantly relies on off-label treatments, often supported by anecdotal reports, single-case studies, or open-label trials. In these contexts, medications are frequently employed as a 'last resort' option, with limited robust clinical evidence to substantiate or guide their use. While the number of RCTs has increased in recent years, these studies often involve small sample sizes and single centers, which restricts their statistical power and generalizability. This highlights an urgent need for large-scale, well-designed controlled clinical trials to establish evidence-based guidelines and improve outcomes for DoC patients [53,82,136].

Multi-center trials are particularly important to account for variability in patient populations, differences in clinical practices, and other confounding factors (e.g. variability in patient populations and clinical practices), ensuring that findings are robust and generalizable [137]. Global collaboration between research groups and medical teams will be necessary to accomplish this goal. To encourage such endeavors, a global registry of current or prospective studies on pharmacological interventions in DoC could be established. Such a platform would help identify opportunities for collaboration, amass larger patient samples, and avoid duplication of efforts. Initiatives like this could catalyze the development of robust, evidence-based treatments for DoC [138].

When considering pharmacological interventions specifically, there is a need for more longitudinal studies, particularly on the long-term administration of drugs, since many studies focus on short-term trials. Even in drugs that appear effective, it remains unclear whether long-term use is advisable and whether there are risks of adverse effects in this unique patient population, where patient heterogeneity already leads to wide discrepancies in injury characteristics and interventions. For example, zolpidem has been reported to lack tolerance effects in some DoC responders [102], while in others, it seems to lose its positive effects on awareness after prolonged administration [95]. Future studies should, therefore, investigate the safety and the efficacy of sustained use of these agents in acute and prolonged DoC patients while aiming to identify and disentangle the individual factors that may influence treatment response. Furthermore, longitudinal studies could explore the potential of using different drugs at various stages of recovery, an area that, to our knowledge, has not yet been thoroughly examined. Identifying stage-specific pharmacological agents could enable tailored interventions that address the evolving neurophysiological dynamics following severe brain injury.

6.2. Earlier intervention

Although pharmacological treatments carry inherent risks, we strongly advocate for more early intervention studies, as early as the acute phase post-injury, when patients are still hospitalized in the ICU or neurological units. Promoting neurological recovery and plasticity during the initial stages of recovery may ultimately outweigh these risks [93,139,140], though further research is certainly warranted to confirm this. Multiple research teams have already shown that such studies are safe and feasible in acute and subacute settings [141–143]. Furthermore, many of the agents discussed in the review are already commonly used in clinical practice and could be studied in the acute phase or repurposed for their therapeutic potential in promoting recovery from DoC. For instance, benzodiazepines are routinely prescribed by clinicians, making it relatively straightforward to assess their impact on consciousness levels using tools like EEG and the CRS-R scale. Collaboration between research teams and clinical staff could facilitate this process, providing valuable data without the need for complex, additional protocols.

6.3. Redefined outcomes

In line with the idea of longitudinal studies, it is important to revisit and refine how we collectively define what constitutes a good outcome in DoC. While some studies assess recovery with a binary approach, (i.e. whether the patient has regained consciousness or the ability to respond to commands), other studies measure more longitudinal outcomes, using (functional) recovery scales (e.g. DRS), while still focusing on specific aspects of physical or behavioral recovery [144]. Consequently, most drugs administered aim to restore wakefulness or responsiveness. Even for the evaluation of short-term changes in consciousness, the tools used may not be up to date. For instance, the CRS-R was developed through consensus over 20 years ago. Since then, the identification of consciousness markers has expanded greatly, now including potential new indicators [145] such as resistance to eye opening [146], eye blinking rate [147], habituation to auditory responses [148], and respiration patterns [149].

While these characteristics are useful objective components for research and statistical analysis, they do not always align with what families perceive as a good outcome. The concept of personhood [150], the idea of reconnecting with the person they were before the injury, seems more important to most families than objective behavioral scores [151,152]. As such, research should aim to further align itself with this understanding: with the goal of promoting recovery that supports the restoration of personhood by emphasizing optimal cognitive recovery and quality of life.

This could be done through the incorporation of scales, like the Quality of Life after Brain Injury scale (QOLIBRI) [153], the Traumatic Brain Injury – Patient Reported Outcome (TBI-PRO) [154], the Life Satisfaction Questionnaire (LiSat-11) [155], the EuroQoL-5 dimensions instrument (EQ-5D-5 L) [156], and the DoC-feeling scale [56,148]. These scales focus on evaluating the subjective quality of life of patients rather than simply objective components [151,157]. In addition, some studies suggest that there may be biological correlates to well-being [158]. In this context, prioritizing interventions that foster long-term recovery and quality of life, rather than focusing solely on immediate responsiveness, is crucial for achieving outcomes that truly matter to patients and their families.

Finally, to achieve better and more meaningful outcomes for patients, it will be crucial to integrate pharmacological approaches with early functional recovery programs and family education. This combined approach could help foster

the recovery of cognitive and motor abilities, ultimately leading to a significantly improved quality of life for patients [139,159,160].

6.4. Unified frameworks

Overall, there is a clear need for well-defined mechanistic and/or functional hypotheses to guide treatment plans and studies, rather than relying on unstructured treatment approaches. Not only would unified frameworks benefit the scientific community by facilitating collaboration and comparison of evidence, but treatment based on pathophysiology and neurological processes would also be more rational, paving the way for personalized medicine. A simple solution could be to reshape clinical studies to focus on the etiology of injury when grouping patients, as it has been shown that etiology and pathophysiology influence recovery rates and response to treatment [161]. However, this approach may not account for all variability. Advances in neuroimaging have enabled the identification of a range of EEG, positron emission tomography (PET), and functional and structural MRI markers correlated with levels of consciousness [14,162–165]. These studies of brain activity have also led to the development of more complex frameworks, which aim to explain patient-specific responses to pharmaceutical treatments. Below are three frameworks that have been proposed to better understand and guide treatment decisions for patients with DoC. Determining the brain's state relative to these frameworks (when possible) could enable a more personalized pharmacological treatment approach.

6.4.1. Mesocircuit hypothesis

The mesocircuit hypothesis offers a compelling framework for explaining the brain response in DoC to various pharmacological compounds, including the paradoxical effects observed with zolpidem [13,20]. For instance, the paradoxical effect of zolpidem may be attributed to its potential to restore the cortico-thalamic inhibition loop [103]. This raises the intriguing possibility that the degree of disruption in this loop may determine the strength of the pharmacological agent required to achieve restoration. Exploring whether the efficacy of different compounds correlates with the extent of cortico-thalamic disruption could shed light on tailoring individual treatments based on specific neural impairments [21]. Figure 3 highlights the main brain regions targeted by this hypothesis, the drugs that could act on them, and their mechanisms of action.

6.4.2. Criticality hypothesis

The critical brain hypothesis stands out and is poised to become a cornerstone of future DoC research. This hypothesis posits that a healthy, awake brain operates near a critical point – a balance between integration and segregation for optimized information processing and high susceptibility to external stimuli [166,167]. Altered states of consciousness are therefore hypothesized to deviate from this equilibrium. For example, sleep and anesthesia are described as 'subcritical' states with increased segregation, whereas sustained wakefulness or epileptic activity represent 'supercritical' states with excessive integration [168]. Given their diverse etiologies, DoC patients could span this spectrum, potentially explaining their varied responses to treatments [166,169]. This framework could transform approaches to pharmacological interventions by identifying the brain's baseline state and selecting agents to guide its activity toward the critical point. For example, given that sedation and anesthesia seem to induce subcritical functioning, sedatives could be used as a potential treatment in a DoC who displays supercritical functioning [168] (Figure 4). Alternatively, psychedelics, which seem to increase criticality, could also be used to improve DoC brain functioning [168,169]. This is only one example of the way frameworks, biomarkers, and clinical data could be combined to refine pharmacotherapy.

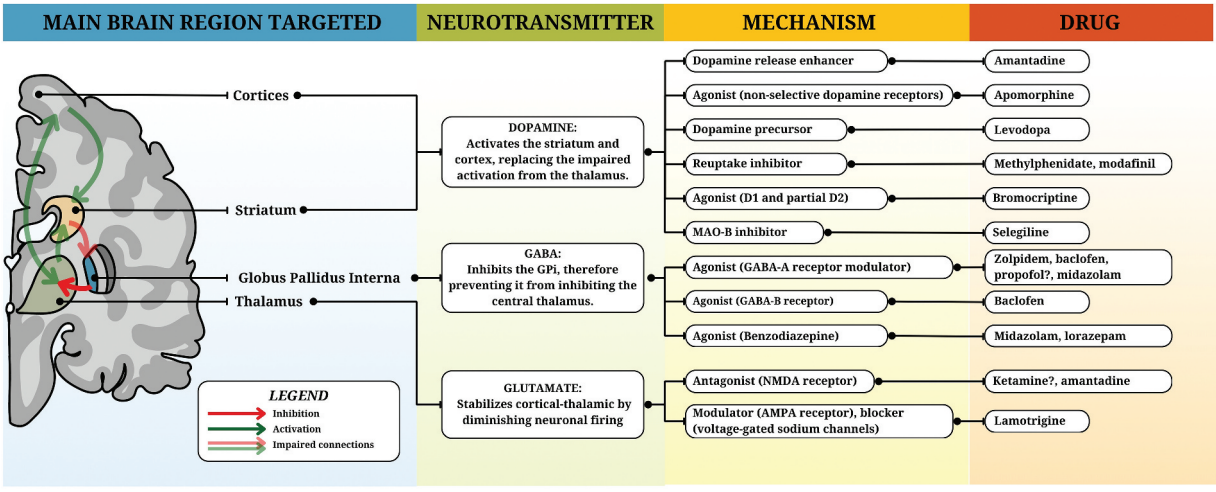

Figure 3. Pharmacological targets according to the mesocircuit hypothesis. This diagram illustrates the key neurotransmitter systems involved in the regulation of consciousness and their associated classes of pharmacological agents. For each neurotransmitter system, different mechanisms of action are highlighted, along with specific agents that may influence thalamocortical and fronto-striatal network activity.

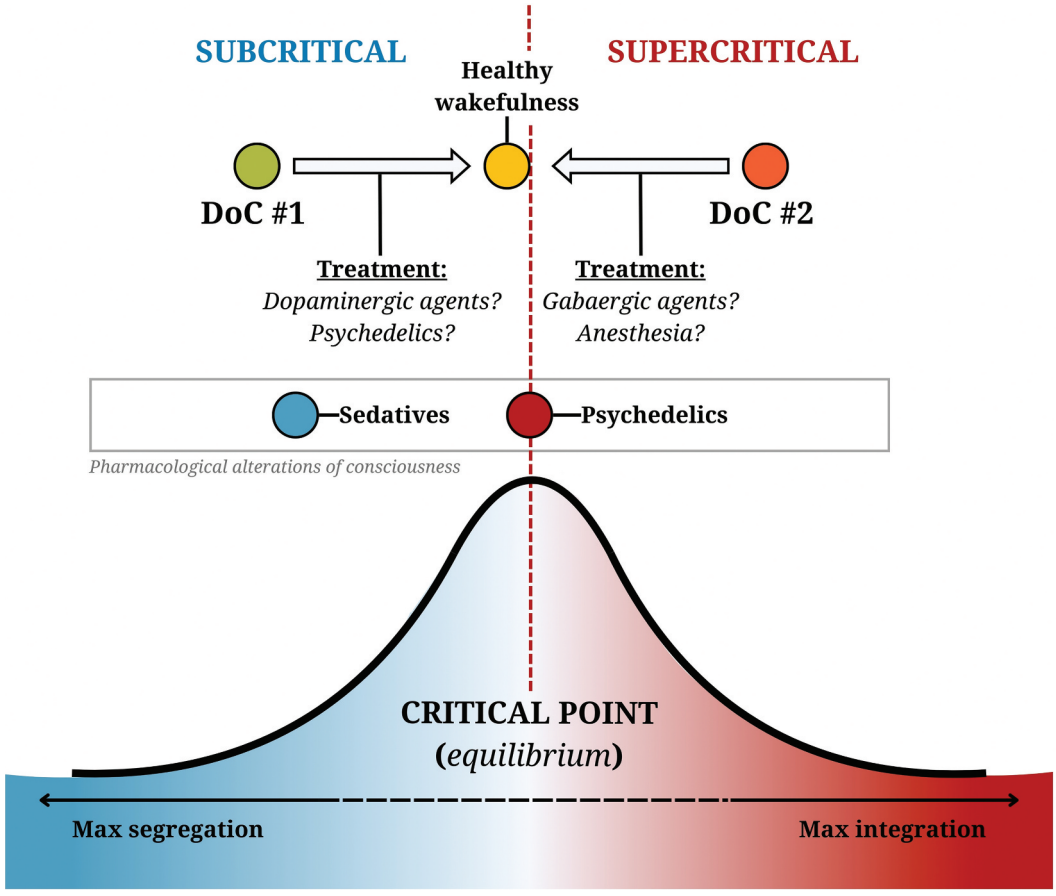

Figure 4. Types of deviations from criticality in disorders of consciousness (DoC) and potential pharmacological treatments. Pharmacological alterations of consciousness (grey box): Healthy awake individuals are believed to operate at an optimal state termed 'near critical' (yellow circle), which represents ideal information processing through balanced integration and segregation. Sedation and anesthesia shift the brain into a 'subcritical' state (blue circle), characterized by reduced integration between brain regions. Conversely, psychedelics can bring the healthy brain closer to the critical point (red dotted line), enhancing complexity and information flow. Types of DoC in relation to the criticality hypothesis: DoC patients may exhibit either 'subcritical' properties (green circle), or 'supercritical' properties (orange circle), where maximal integration disrupts effective functioning. Based on the criticality hypothesis, we could potentially aim to restore criticality in the brain by identifying whether a DoC patient presents sub– or super–critical properties, and subsequently identifying the appropriate pharmacological intervention to shift the brain in the appropriate direction (white arrows).

6.4.3. Neural complexity

Neural complexity is hypothesized to be a necessary feature for the emergence of consciousness [170–173] and is also thought to be a feature of a brain operating in a critical state. Brain signals recorded from EEG or fMRI display a high degree of complexity, which reflects the dynamic interactions among various brain regions. A signal exhibiting high complexity cannot be easily decomposed into independent components, indicating that it arises from the integrated activity of multiple brain networks rather than from isolated sources [170]. In the case of EEG, the recorded activity reflects the interactions of several networks, such as the thalamocortical loop and fronto-parietal networks. In the context of the mesocircuit model, if the thalamus is 'isolated' following brain injury, it is expected to generate a much less complex signal [174,175]. This reduction not only informs us about the level of consciousness but may also provide insights into the pathophysiology of DoC, particularly the extent of thalamocortical impairment. Overall, identifying drugs that target these mechanistic and functional frameworks holds great promise. For instance, psychedelics have been shown to increase complexity in healthy individuals [176,177]. Since unconscious states, like DoC, are associated with reduced complexity [174,178,179], administering psychedelics may potentially enhance complexity and, in turn, help restore some degree of consciousness [169,180].

Among these concepts, criticality and neural complexity offer definitive advantages as they can be quantified through electrophysiology, unlike the mesocircuit model, which provides an explanation for treatment response but is difficult to evaluate through EEG.

6.5. Personalized medicine

Given the diversity of the DoC patient population, a one-drug-cures-all approach is not suitable. Aside from the varied etiologies, the broad age range affected, and known sex differences in drug response [181], one critical factor is that the injured brain does not respond to pharmacological compounds as the healthy brain does because of factors such as disruption of the blood brain barrier, neurotransmitter imbalances and neuroinflammation [182–184]. Indeed, many injury-related factors (e.g. location, extent, time since injury,

complications) are likely to modulate the brain's response to these agents in ways that are not fully understood nor entirely predictable.

Additionally, genetics have been broadly proposed to play a role in patients' recovery and therapy responsiveness [185,186]. Paradoxical responses to zolpidem have been reported in various populations, including those with neurological, psychiatric, sleep, and alcohol-related disorders, as well as in healthy individuals [187–193]. Instead of the expected sedative effect, these individuals experienced increased arousal, euphoria, agitation, and craving after taking zolpidem [193–195].

Overall, the combination of the aforementioned factors stresses the need to shift to personalized medicine and to innovate when thinking of new therapeutic perspectives, perhaps even going for more 'counterintuitive' treatments.' Advancements in artificial intelligence (AI) have opened new possibilities for identifying individual factors attributable to treatment success [196]. By leveraging neuroimaging and clinical data, AI could model these complex drug responses and optimize treatment strategies for individual patients [197,198]. This technology has the potential to reduce patient risk by allowing accurate simulations of pharmacological effects prior to drug administration, thereby compensating for the current lack of reliable preclinical models of DoC [199]. Recent studies have shown that, in healthy participants undergoing anesthesia with propofol, xenon, or ketamine, predicting the effect of the drug on the level of consciousness is feasible through the measurement of baseline neuroimaging biomarkers like avalanche criticality and chaoticity [200]. By identifying the baseline brain state of a patient, we could then choose treatment accordingly [201]. Future research using machine learning approaches could identify the combination of factors (e.g. demographic, etiology, genetic variations, brain-based biomarkers, EEG features [critical state, complexity], and behavioral level of responsiveness) that can best predict responsiveness to treatment. This, in turn, could facilitate the development of personalized treatment protocols, enabling clinicians to move beyond a trial-and-error approach toward a more data-driven strategy for managing DoC. Such approaches could also help stratify patients into more homogeneous subgroups, improving the accuracy of clinical trials and reducing variability in treatment outcomes. Moreover, real-time monitoring of neurophysiological markers, combined with adaptive machine learning models, could allow for continuous adjustment of therapeutic interventions based on the patient's evolving brain state. Ultimately, integrating AI-driven predictive tools into clinical practice has the potential to revolutionize DoC management, increasing the likelihood of recovery and offering more targeted and effective care.

6.6. New pharmacological avenues

In addition to the conventional, relatively well-established drugs discussed in previous sections, numerous pharmacological compounds remain underexplored or entirely unexplored in this population [180,202–208]. In the following section, we will discuss the rationale for investigating these compounds further in specific contexts, focusing on their potential mechanisms of action and how they could contribute to improving outcomes for DoC patients. We will use the mechanistic and functional frameworks to speculate on how these drugs might be of use.

6.6.1. Propofol

Propofol, a commonly used sedative in anesthesia and critical care settings, is a GABAergic agonist that binds preferentially to GABA-A receptors. Due to its similarity to zolpidem in mechanism of action, propofol is currently being investigated in acute settings to determine whether it might also induce paradoxical response in DoC patients [200,202,203,209,210]. Some studies on zolpidem suggest a potential dose-response relationship, with higher dosage associated with increased response rates [98,211]. This raises the possibility that the profound disruptions of neural networks observed in severely injured brains may require stronger agents, such as propofol, to reestablish functional dynamics temporarily. This is also supported by the mesocircuit hypothesis: like zolpidem, the activation of GABA receptors in the globus pallidus interna would allow the disinhibition of thalamocortical pathways. Furthermore, studies in criticality have shown that healthy participants under propofol anesthesia are in subcritical states. Thus, even if propofol does not induce paradoxical effects on the brain or behavior, it has been hypothesized that sedatives may help supercritical DoC patients return closer to the critical point, potentially restoring normal brain dynamics. Moreover, a recent study in mice suggests that propofol might have neuroprotective effects on TBI by modulating the endothelial nitric oxide synthase-nitric oxide (eNOS-NO) signaling pathway, which is involved in neuroinflammation following injury [212]. Despite its potential benefits, the use of propofol is not without significant risks. Adverse effects can include cardiorespiratory depression, hypotension, and propofol infusion syndrome, particularly with prolonged or high-dose administration. Given these risks, its use in DoC patients must be approached with caution and always conducted in highly controlled medical settings, with continuous monitoring. However, it is frequently used for light sedation in patients with DoC undergoing MRI examinations, presenting an opportunity to study its effects. Its use could potentially be light and intermittent in a controlled medical setting. While propofol may offer a promising avenue for restoring functional dynamics in severely disrupted brain states, further research is necessary to determine its safety, optimal dosing, and long-term impact on recovery in this vulnerable population.

6.6.2. Psychedelics

Psychedelics are a class of psychoactive substances that alter perception, mood, and cognitive processes, often inducing profound changes in sensory experiences and consciousness by acting primarily on serotonin receptors in the brain. Well-known agents in this category include psilocybin, lysergic acid diethylamide, and N, N-Dimethyltryptamine. Ketamine, though acting on glutamatergic transmission through NMDA receptors, is also considered an (atypical) psychedelic agent at subanesthetic doses. Psychedelics have recently been recognized for their potential in the treatment of a variety of psychiatric conditions [213]. Importantly, studies have also

shown that psychedelics bring brain dynamics closer to the critical point than healthy wakefulness [168]. It has also been shown that psychedelics enhance complexity in the healthy brain [176,214,215], suggesting their potential ability to also increase brain complexity in DoC [168,180,206].

Following this rationale, psychedelics could have potential in treating subcritical DoC states and increasing complexity, potentially providing improved conditions for sustaining consciousness. Following these theoretical foundations, a double-blind, placebo-controlled, crossover trial investigated the use of a sub-anesthetic dose of ketamine in three adult patients with chronic DoC (2 MCS and 1 UWS) [206]. While no changes were observed in behavioral measures of consciousness using the Simplified Evaluation of CONsciousness Disorders (SECONDs) scale, spasticity was found to decrease, and brain complexity was higher during ketamine sessions compared to placebo. Similarly, a recent case report on the use of psilocybin in an MCS patient showed no increase in overt behavioral repertoire using validated scales [205]. Yet new spontaneous behavior was observed (i.e. moving the legs), and an increase in brain complexity, as measured by the Lempel-Ziv complexity, was also identified. These two preliminary studies suggest that following psychedelics intake, these patients may have been disconnected from the environment (as they were unable to respond to command), but they might still have had an internal experience (as their brain complexity increased) [205]. While the current literature on psychedelics in DoC remains sparse, it reflects a growing openness to exploring less conventional pharmacological approaches and unlocking new avenues for treating a condition with limited options. Additionally, psychedelics, or more broadly, psychoceuticals, are varied in nature and targets: a recent review of the literature identified 20 compounds with psychedelic-like effects. This diverse array of drugs capable of altering conscious experience offers promising avenues to be explored as treatment [216]. However, research on psychedelics remains challenging, as access to substances like psilocybin is restricted to a few countries in Europe and North America, limiting the feasibility of multicentric studies. Rigorous RCTs are essential to generate robust evidence that could inform regulatory changes and expand research opportunities. Ethical concerns, particularly regarding studies involving DoC patients unable to provide explicit consent, are significant [169,180,217]. However, given the established safety profiles of these substances [218] and the use of supportive experimental settings [219], such trials can be ethically justified when conducted under strict oversight. These efforts are crucial to advancing both clinical applications and the understanding of psychedelics in this unique population.

6.6.3. Saxagliptin

Saxagliptin, a dipeptidyl peptidase-4 inhibitor primarily used as a diabetes medication, is currently being explored for its potential in consciousness recovery. A deep-learning -based drug screening model identified saxagliptin as a candidate for restoring consciousness based on its three-dimensional molecular structure [204]. This hypothesis is further supported by evidence suggesting that incretin-based diabetes medications are associated with higher coma recovery rates compared to other diabetes treatments [204]. While no human trials have been published yet, preclinical studies suggest that saxagliptin may positively impact neurotransmission, neuroinflammation, and oxidative damage [204]. This example highlights how advanced technologies, such as deep learning phenotypic drug screens, can open new avenues for pharmacotherapy. By identifying treatments that might not have been considered otherwise, these technologies enhance our ability to discover novel therapeutic options, potentially improving patient outcomes in unexpected ways.

6.6.4. Combination therapies

Certainly, the potential synergistic effects of some drugs warrant exploration, as combination therapies might yield better outcomes for DoC than single agents. However, seeing as though rigorous studies are already lacking for drugs used on their own, there are not a lot of studies on combination therapies in DoC. Amantadine has been used in combination with other pharmacological agents. A study on 84 patients with acute, subacute, and chronic DoC due to mixed etiologies compared amantadine (single regimen) to amantadine plus cerebrolysin (dual regimen). The results showed that both single and dual regimens led to recovery of consciousness as assessed by CRS-R. However, more behavioral changes, a higher number of favorable changes in the clinical diagnosis, and a larger proportion of patients with significant behavioral changes were found in the dual regimen group [220]. Although the literature on this topic is limited, there is significant potential. With a personalized medicine approach and a deeper understanding of the underlying pathophysiology of DoC, this could become a promising area of research.

Another aspect of combination therapies is the combination of pharmacological treatment with other approaches, like repetitive transcranial magnetic stimulation (rTMS) or rehabilitation programs [93,221]. For instance, amantadine, combined with rTMS, was studied in four chronic DoC patients (TBI-induced, UWS, MCS-) over 28 days. The results showed neurobehavioral and auditory-language improvements in all, with those receiving rTMS first showing greater gains. All patients were diagnosed as MCS, with treatments modulating functional connectivity in language, salience, and sensorimotor networks [221]. As mentioned above, when zolpidem was administered to a DoC responder as part of a tailored multimodal intervention program, it appeared to enhance patient outcomes significantly [93]. This also aligns with the concept of earlier intervention, suggesting that such combined therapies may foster neuroplasticity and offer the potential for improved long-term functional recovery [93].

6.7. Vision

While research on pharmacological interventions for DoC is steadily expanding, significant gaps in the literature continue to limit progress. To advance to the next era of pharmacological treatment of DoC, several key changes are essential.

Personalized medicine must become a priority, with pharmacological interventions tailored to individual patient characteristics, supported by robust, collaborative frameworks that target mechanistic and functional pathways. Additionally, there is an urgent need for more comprehensive clinical trials, not only to strengthen the evidence but also to refine treatment protocols, unify research efforts, and foster innovation. These trials should expand beyond the chronic DoC population and explore the potential benefits of early interventions, which may offer a greater chance for recovery. Finally, the concept of a 'good outcome' must evolve, shifting the focus from short-term improvements to long-term quality of life and functional independence. Moving forward, assessing the efficacy of more unconventional or 'paradoxical' pharmacological options in treatment plans will be essential. In parallel, we envision a stronger implementation of AI tools to identify factors that best predict treatment responses based on demographics, injury characteristics, genetics, and brain-based biomarkers. By integrating these advancements, the field can move toward more precise, evidence-based therapies that offer meaningful, long-lasting improvements for individuals with DoC, ultimately bridging the gap between research and personalized clinical care.

Abbreviations

CAM-ICU	Confusion Assessment Method for the intensive care unit
CNCS	Coma/Near-Coma Scale
CRS-R	Coma Recovery Scale-Revised
DoC	Disorders of consciousness
DRS	Disability Rating Scale
EEG	Electroencephalography
FDA	Food and Drug Administration
FIM^{TM}	Functional Independence Measure
fMRI/MRIimaging	Functional magnetic resonance imaging/ Magnetic resonance
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
LOCFAS	Level of Cognitive Functioning Assessment Scale
MAOB	Monoamine oxidase-B
MCS	Minimally conscious state
MRS	Modified Rankin scale
NMDA	N-methyl-D-aspartate
PET	Positron emission tomography
SSRIs	Selective serotonin reuptake inhibitors
TBI	Traumatic brain Injury
TCA	Tricyclic antidepressants
UWS/VS	Unresponsive wakefulness syndrome/Vegetative state
WHIM	Wessex head injury matrix

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