Pharmacotherapy in disorders of consciousness: a mechanism-based review

Running title: Pharmacotherapy in Disorders of Consciousness

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Abstract

Disorders of consciousness (DoC) pose major therapeutic challenges due to the complexity of underlying brain dysfunctions. Current pharmacological interventions explored in DoC target distinct molecular systems, including dopaminergic modulators (amantadine, levodopa, apomorphine, bromocriptine, selegiline, methylphenidate, and modafinil), GABAergic agents (zolpidem and baclofen), and other neuromodulatory compounds acting on glutamatergic, opioid, or serotonergic receptors (ketamine, remifentanil, and psilocin). These treatments aim to modulate disrupted neural circuits, including the mesocircuit, a thalamocortical-striatal network critically involved in consciousness and motor control. This review explores the pathophysiological mechanisms underlying DoC and the pharmacological profile of these agents. It summarizes reported clinical improvements and discusses determinants of therapeutic response, highlighting the role of biomarkers derived from neurophysiological and neuroimaging assessments. Safety profiles associated with these treatments are also critically evaluated to guide clinical decision-making. By integrating current knowledge on pharmacological modulation of key neural systems, including dopaminergic and GABAergic pathways, this article provides a comprehensive framework for understanding treatment strategies in DoC.

Key points

- The current landscape of pharmacological treatments for disorders of consciousness focuses on modulating key neural circuits, such as the mesocircuit.
- Various agents targeting different molecular pathways have been tested, including dopaminergic modulators, GABAergic agents, and other neuromodulatory compounds acting on glutamatergic, opioid, or serotonergic receptors.
- This review summarizes their mechanisms of action, clinical outcomes, and safety profiles, while highlighting the importance of neuroimaging and neurophysiological biomarkers in predicting therapeutic response.

1. Introduction

Following a severe brain injury, patients may enter a disorder of consciousness (DoC). These alterations in consciousness can be classified into distinct states. Coma is defined by a persistent lack of eye opening, lasting for more than one hour [1]. The unresponsive wakefulness syndrome (UWS), also coined as "vegetative state" (VS) is characterized by preserved eye opening, autonomic functions, and generally preserved sleep-wake cycles [2]. In contrast, the minimally conscious state (MCS) reflects a higher level of consciousness, marked by inconsistent but reproducible signs of awareness and encompasses two distinct profiles: MCS- and MCS+, which differ based on the absence (MCS-) or presence (MCS+) of residual language-related abilities [3]. A patient is characterized as having emerged from the MCS (EMCS) by their ability to functionally use objects and/or functionally communicate. A patient who remains in a DoC for more than 28 days is currently considered to be in a prolonged or chronic state of impaired consciousness [4]. Approximately 5 per 100,000 individuals enter a prolonged DoC each year, though the true prevalence may be underestimated [5]. Some patients may remain in a DoC for months or even years. It is therefore crucial to explore treatment options, including pharmacological approaches.

A proposed theoretical framework to account for prolonged DoC is the fronto-parietal mesocircuit model (Figure 1), which suggests that a feedback communication loop between several brain structures, including the frontal and parietal cortices, striatum, pallidum, and central thalamus (particularly the central lateral and parafascicular nuclei), is essential for maintaining consciousness [6]. In this model, thalamocortical projections from the central thalamus (particularly the central lateral and parafascicular nuclei) provide strong excitatory drive to both cortical pyramidal neurons and striatal medium spiny neurons (MSNs). The MSNs in turn exert inhibitory control over the globus pallidus (GPi), which normally provides tonic inhibitory output to the central thalamus. Adequate MSN firing rates require both sustained excitatory synaptic input and dopaminergic neuromodulation; widespread deafferentation or loss of cortical drive leads to reduced MSN activity, resulting in excessive GPi inhibition of the thalamus and a global downregulation of anterior forebrain activity. This cascade can manifest as a shutdown of the fronto-parietal networks necessary for consciousness. This model posits that three major mechanisms may underlie dysfunction of the forebrain: widespread neuronal death, generalized deafferentation, and circuit-level functional disturbances.

This model also provides an explanation for how pharmacological agents could potentially restore levels of consciousness in some patients by acting over different levels of the model. So far, amantadine is the only medication recommended for the treatment of DoC by international guidelines [4]. However, several pharmacological therapies are currently being explored, including dopaminergic agents (e.g., apomorphine [7], levodopa [8]), gamma-aminobutyric acid (GABA) agonists (e.g., zolpidem [9], baclofen [10]), and serotonergic agents (e.g. psilocin [11]). The aim of this review is to examine the current state of the science regarding pharmacological interventions proposed for DoC patients, with a particular focus on their mechanisms of action within the mesocircuit theory hypothesis.

2. Literature search strategy

In this narrative review, the primary literature search was conducted in PubMed, a comprehensive biomedical database, using a Boolean query targeting pharmacological treatments in patients with DoC. Additional relevant articles were identified through manual screening of the reference lists of included studies and key review papers. The search was the following: ("Drug therapy"[MeSH Terms] OR "Pharmaco Treatment"[tw] OR "Medical Treatment"[tw] OR "Amantadine"[tw] OR "Apomorphine"[tw] OR "Levodopa"[tw] OR "Methylphenidate"[tw] OR "Bromocriptine"[tw] OR "Modafinil"[tw] OR "Selegiline"[tw] OR "Zolpidem"[tw] OR "Baclofen"[tw] OR "Psychedelics"[tw]) AND ("apallic syndrome"[tw] OR "apallic syndromes"[tw] OR "consciousness disorder"[tw] OR "consciousness disorders"[tw] OR "consciousness disorders"[mesh:noexp] OR "disorder of consciousness"[tw] OR "disorders of consciousness "[tw] OR "minimally conscious state"[tw] OR "minimally conscious states"[tw] OR "prolonged loss of consciousness"[tw] OR "unawareness state"[tw] OR "prolonged unawareness"[tw] OR "prolonged posttraumatic unawareness"[tw] OR "prolonged post traumatic unawareness"[tw] OR "unresponsive wakefulness syndrome"[tw] OR "unresponsive wakefulness syndromes"[tw] OR "vegetative state"[tw] OR "vegetative states"[tw] OR “higher order cortex motor dissociation"[tw] OR “HMD"[tw] OR “cortex motor dissociation"[tw] OR “CMD"[tw] OR “covert awareness"[tw])

This strategy yielded a total of 700 articles. Based on title and abstract screening, 594 articles were excluded. An additional 41 articles were excluded after full-text review. In total, 67 articles were retained for data extraction and analysis. We chose to include original research articles reporting empirical results (either from group studies or single case reports) focusing on adult patients with DoC.

3. Overview of current evidence

The reviewed literature comprises a heterogeneous set of studies, including case reports [12–44], pilot trials [45–48], retrospective cohort studies [10,49–54], prospective (open-label) studies [7,9,50,55–65], and randomized controlled-trials [66–69], involving up to 442 individuals. Regarding etiology, the most commonly reported causes of DoC were traumatic brain injury (TBI) [7,9,10,13,17–19,21,22,24,25,27,31–33,38,38–40,42,43,45,49,52–59,61–63,65–67,69–74], anoxic brain injury [11,31,35,36,43,48,51,52,56,61,62,64,65,67,68] and stroke (both hemorrhagic and ischemic) [14,20,26,28,36,37,40,41,49,50,53,68,69,75]. Other etiologies such as autoimmune encephalitis (e.g., Anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis) [29] and subarachnoid hemorrhage (SAH) were less frequent [14,20,28,36,41,53,68]. The time since injury at treatment initiation varied considerably across studies, ranging from a few weeks to over a decade. Various pharmacological agents were evaluated, including dopaminergic agents (Table 1; amantadine, apomorphine, levodopa, methylphenidate, modafinil, bromocriptine, selegiline), Gamma-aminobutyric acid modulators (Table 2; baclofen, zolpidem), and other pharmacological agents (Table 3; remifentanil, ketamine and psilocin). These were either administered alone or in combination with other therapies. For each of these pharmacological agents, we will present their underlying pathophysiological mechanisms, reported clinical improvements, lack of efficacy in some cases, determinants of response, safety profiles, and potential biomarkers (when available).

3.1. Dopaminergic agents

3.1.1. Amantadine

Amantadine was initially developed as an antiviral therapy and is still approved as prophylactic treatment of influenza A and related respiratory infections. While it is currently less used due to the development of other therapeutics, it remains approved by the United States Food and Drug Administration (FDA) for the treatment of Parkinson's disease and neuroleptic-induced parkinsonism. Since 2018, it is also recommended for use in patients with DoC according to the Practice Guideline Update Recommendations of the American Academy of Neurology [4] : amantadine (100–200 mg twice daily) should be prescribed for adults in an UWS or MCS between 4 and 16 weeks post-traumatic injury, in order to accelerate functional recovery and reduce early disability.

3.1.1.1. Pathophysiological mechanisms

Amantadine enhances dopamine function both presynaptically, by inhibiting dopamine reuptake and facilitating dopamine release, and postsynaptically, by increasing the number of dopamine receptors [50]. These effects are particularly relevant in brain regions such as the nigrostriatal, mesolimbic, and frontostriatal circuits, which are critical for arousal, motivation, and attentional processes [66]. In the context of TBI, diffuse axonal damage often leads to reduced dopamine turnover. By promoting dopaminergic neurotransmission, amantadine may help compensate for this deficiency and facilitate recovery of sensory and higher-order cognitive functions.

3.1.1.2. Reported clinical improvements

Across cases reports [13–19], observational cohorts [49–51,54,56,76], and controlled trials [45,66,68], amantadine (from 50mg to 400mg twice per day) has consistently been linked to accelerated recovery of consciousness. One of the most striking features across studies is the rapidity of clinical response: improvements are often noted within the first week of treatment, sometimes even within days [16,50,51,68].

In 2012, a large randomized controlled trial (n=184) showed that patients who received amantadine achieved faster recovery trajectories and higher scores on the Disability Rating Scale (DRS) than those receiving placebo [66]. More specifically, amantadine intake led to functional recovery, as patients in the experimental group were found to be more likely to regain functional object use, reliable yes/no communication or purposeful motor responses compared to the placebo group [66].

Other studies confirmed these results, showing clinical improvement rates ranging from 50 [66] to 100% [50] in patients receiving amantadine. A retrospective study (n=442) in the Intensive Care Unit demonstrated that 60.4% exhibited am improvement in their Glasgow Coma Scale (GCS) score by three points or more within a five-day treatment period [51].

Furthermore, a retrospective study (n=84) evaluated single (amantadine alone) versus dual regimens (amantadine combined with cerebrolysin, a porcine-derived neuropeptide preparation that exerts neuroprotective and neurotrophic effects by reducing excitotoxicity and neuroinflammation [77]). Their results indicated that both groups showed Coma Recovery Scale-Revised (CRS-R) improvements and shifts in diagnostic category (e.g.,

from VS to MCS), with the dual regimen leading to greater gains, especially in visual and oromotor/verbal functions [49].

3.1.1.3. Lack of improvement and determinant of response

However, while case studies reported initial clinical improvements during amantadine treatment these effects often appeared to be short-lived and reversible [20, 30]. Behavioral gains typically coincided with periods of active drug administration and diminished once the treatment was discontinued [76], suggesting a dose-dependent but transient effect [19]. Moreover, case studies [15,18] and a double blind placebo-controlled study (n=37) [68] could not demonstrate any clear bedside behavioral improvement that could be specifically attributed to amantadine treatment.

A retrospective controlled study (n=46) showed that patients with hemorrhages in the thalamus or basal ganglia responded better to amantadine than those with lesions in the frontal-temporal-parietal regions [43]. This indicates that the site of brain injury might determine treatment responsiveness. Some studies raise the possibility that amantadine may play a neuroprotective role rather than enhancing consciousness directly [68]. Finally, some analyses reported that earlier treatment does not necessarily yield better outcomes. In fact, the treatment effect was more pronounced in patients enrolled later, possibly suggesting that amantadine might "jump-start" recovery in select individuals [66]. However, the lack of clear dose-response relationships and presence of spontaneous recovery patterns obscure the interpretation of efficacy.

3.1.1.4. Safety profile

Although amantadine has a good safety profile, several studies have reported adverse effects that may limit its use or require dose adjustments. These effects range from tachycardia [28, 29] to facial myoclonus [19] sleep disturbances, diarrhea, and skin rash, although these were typically mild and responsive to symptomatic treatment [50]. In a double blind placebo controlled study, 10.5% (n=4) of patients experienced potential drug-related adverse events such as seizures, paralytic ileus, or tachycardia, though not all were confirmed to be directly caused by amantadine [68]. Responders (improvement in the GCS score by ≥ 3 points within a five-day treatment period) and non-responders experienced similar overall complication rates, with seizures more frequent in non-responders and delirium more common in responders, while cardiac arrhythmias occurred in both groups [51]. Importantly, in Giacino et al. (2012), the incidence of adverse events did not significantly differ between the amantadine and placebo groups, and no increased risk of seizures, cardiovascular complications, or other major concerns was observed [66]. However, an International Suvey highlighted the fact that some clinicians remain hesitant to use amantadine due to concerns about a possible association with epileptic seizures [78], despite the lack of consistent evidence in the literature supporting such a link [79]. An important point however is that given that amantadine is primarily excreted unchanged in the urine, its pharmacokinetics are strongly influenced by renal function, making dose adjustment essential in patients with renal impairment to avoid drug accumulation and adverse events [80].

3.1.1.5. Biomarkers

A case study and a retrospective study (n=44) identified EEG changes as potential markers of amantadine efficacy [31, 34]. Higher frontocentral gamma (30-50 Hz) and beta (14-29 Hz) frequencies before treatment were linked to better command following recovery [54]. After seven days of treatment, EEG patterns indicating greater corticothalamic integrity predicted behavioral improvement, with all patients showing these patterns regaining command following before discharge. An increase in alpha frequency (7–8 Hz to 10–11 Hz) during treatment was also noted, suggesting enhanced cortical arousal [19].

In a retrospective study (n=442) involving, pathological brain imaging, including acute ischemic stroke, intracranial cerebral hemorrhage, hypoxia, microangiopathy, and old lesions, was identified as potential biomarkers associated with a reduced likelihood of response to amantadine treatment, as well as cardiac arrest [51]. Additionally, the presence of a posterior dominant rhythm (PDR) prior to treatment correlated with better outcomes [51]. The "ABCD" (electroencephalography) EEG model showed hierarchical improvement in command following, peaking near 80% in patients with pattern D.

Physiologically, patients on amantadine exhibited higher baseline skin conductance responses and elevated electromyogram (EMG) activity, indicating increased cortical arousal likely mediated by the reticular activating system [56]. Functional Magnetic Resonance Imaging (fMRI) studies demonstrated increased activation in multiple brain regions during and after treatment, with expanded responses to familiar auditory stimuli after three months, suggesting restored sensory processing and cognitive function[17]. Resting-state fMRI revealed amantadine reduced connectivity between key brain networks (Default Mode Network, Salient Network, Sensorimotor Network), possibly normalizing hyperconnected or disorganized networks associated with neurobehavioral improvement [45]. Positron Emission Tomography (PET) studies showed increased glucose metabolism in prefrontal and parietal cortices, especially the left dorsolateral prefrontal cortex[15].

3.1.2. Apomorphine

Apomorphine is a non-selective dopamine agonist that primarily stimulates D1 and D2 receptors [81]. Although it is currently marketed and widely used as a dopaminergic treatment for Parkinson’s disease, some studies have highlighted its potential efficacy in promoting recovery of consciousness in patients with DoC [7,12,57,67].

3.1.2.1. Pathophysiological mechanisms

The rapid and complete absorption via continuous subcutaneous infusion allows for constant stimulation of dopaminergic pathways, compensating for its poor oral bioavailability [7]. In the context of DoC, apomorphine’s pharmacodynamic properties are particularly relevant: its direct action on dopamine receptors may better address presynaptic dopamine depletion [81]. Furthermore, its high affinity for D2 receptors, which are abundantly expressed in striatal medium spiny neurons, may facilitate the restoration of dysfunctional striato-pallidal efferent pathways [82]. This targeted action supports the reactivation of cortico-striato-thalamo-cortical loops, which are critical for arousal and conscious processing, and may underlie the therapeutic potential of apomorphine in promoting recovery of consciousness in DoC patients.

3.1.2.2. Reported clinical improvements

Two studies [7,57] and a case report [12] have reported promising effects of apomorphine (for 12 hours/day, using a dose escalation infusion rate from 2mg/h to 8mg/h) on the recovery of consciousness in patients with prolonged DoC [10-12]. In a controlled trial, patients treated with apomorphine (n=6) showed significantly greater improvements in behavioral diagnosis compared to controls (n=7) with three out of six patients changing diagnostic category during the intervention and four out of six maintaining improvement at 6- and 12-month follow-ups [7]. All patients in the apomorphine group increased their CRS-R index scores across phases, and 83% exhibited new conscious behaviors, including language-related functions (50% of apomorphine patients vs. 14% in controls). Additional open-label work reported rapid progression from simple command-following to functional communication, orientation, independent ambulation and even full recovery of autonomy in some cases [12,57]. Notably, symptom relapse upon treatment interruption and subsequent recovery upon reinstatement further support a causal relationship. In a randomized, placebo-controlled trial in brain injury patients with acute DoC (n=50), administration of apomorphine was associated with a change toward a higher consciousness level category in four patients (although group-level effects did not reach statistical significance) [67]. Additionally, apomorphine was linked to temporary improvements in arousal, suggesting that it may have clinically meaningful effects in individual patients [67]. These converging findings underscore the potential of apomorphine to elicit both early and sustained behavioral and cognitive recovery in DoC patients.

3.1.2.3. Safety profile

Across the reported studies, apomorphine treatment was generally well tolerated, with no severe or treatment-limiting adverse effects directly attributed to the drug. In the controlled trial, all six patients experienced vomiting, which was effectively managed with antiemetics and dosage adjustments [7]. Other common side effects included skin erythema (in 4 out of 6 patients) and local skin nodules (1 patient), both of which were resolved through infusion site rotation and local care, without the need to interrupt treatment. In the case report, mild focal dyskinesias, sporadic penile erections, and a single episode of hallucination (occurring off-medication) were observed when the apomorphine dose reached 8mg/h; all symptoms resolved upon dose reduction to 6mg/h [12]. Overall, these findings suggest that while mild side effects are relatively common, they are predictable, manageable, and reversible, indicating a favorable safety profile of apomorphine in DoC patients.

3.1.2.4. Biomarkers

Sanz et al. (2024) reported neuroimaging and electrophysiological data that revealed biomarkers associated with apomorphine treatment in DoC patients. High-density electroencephalography (hdEEG) analyses showed a significant increase in functional connectivity in the alpha frequency band, both at the whole-brain level and specifically in parieto-temporal interactions [7]. Additionally, the alpha network participation coefficient (a measure of integrative network dynamics) was significantly enhanced post-treatment across the whole brain, particularly in frontal regions, indicating improved global integration [7]. No significant changes were observed in spectral power or connectivity in other frequency bands. Metabolic changes measured via fluorodeoxyglucose-PET showed a mean global Standardized Uptake Value (SUV) improvement of 13.8% post-treatment [7], suggesting a partial restoration of brain metabolism.

3.1.3. Levodopa

Levodopa is a metabolic precursor of dopamine [83] and is widely used as a dopaminergic agent in the treatment of Parkinson's disease [84], several studies have also highlighted its potential to promote recovery of consciousness in DoC patients [20,55,58,70].

3.1.3.1. Pathophysiological mechanisms

Levodopa acts as a dopamine precursor capable of crossing the blood–brain barrier, where it is converted into active dopamine [85]. Co-administration with carbidopa prevents peripheral metabolism, increasing central availability [84]. By enhancing dopaminergic transmission in fronto-striatal and thalamo-cortical pathways [6], levodopa may help restore neural circuits critical for motor responsiveness and conscious awareness.

3.1.3.2. Reported clinical improvements

A case study [20] and small clinical series [44,55,58,70] have reported meaningful improvements in consciousness following levodopa administration (with a dose from levodopa 100mg/day + carbidopa 24mg/day to levodopa 750mg/day + carbidopa 75mg/day). In one case, a patient with no prior extrapyramidal signs exhibited spontaneous eye opening and limb movement just four days after initiating levodopa/carbidopa therapy, followed by progressive verbal recovery and the ability to interact using hand signs [20]. Tapering the medication led to regression, which reversed upon resuming the initial dose, suggesting a direct therapeutic effect. Across other reports, initial improvements typically emerged within the first two weeks of treatment (often as early as four to ten days) and consistently followed a pattern: obeying simple motor commands (e.g., limb movement), followed by more complex tasks like responding to two-step commands and engaging in reciprocal interactions [55]. In one study (n=8), 7 patients regained consciousness after approximately one month of levodopa treatment [58]. Another case series (n=3) reported patients recovering verbal communication, walking with support, and even using devices to express thoughts, with some maintaining long-term benefits requiring continued levodopa use [70].

3.1.3.3. Lack of improvement and determinant of response

The clinical response to levodopa in DoC appears to be influenced by several key factors. While reported cases of improvement have occurred following TBI, emerging evidence suggests that dopaminergic treatment can also be effective in non-TBI etiologies, such as hemorrhagic events, even in the absence of parkinsonian features [20]. Notably, patients with signs of extrapyramidal dysfunction or MRI findings indicating lesions in dopaminergic structures (e.g., substantia nigra, ventral tegmentum, or basal ganglia) appear more likely to benefit [70]. These findings highlight the need for individualized treatment considerations based on clinical signs and neuroimaging biomarkers when assessing levodopa responsiveness [70].

3.1.3.4. Safety profile

Adverse effects related to levodopa administration in patients with DoC appear to be rare [20,44,55,58,70]. Among the reviewed studies, one patient (out of 8) experienced visual hallucinations following the administration of three tablets per day (levodopa 750mg/day + carbidopa 75mg/day) [58]. This symptom resolved completely after dose reduction (levodopa 187.5mg/day + carbidopa 18.75mg/day), and the patient kept improving.

3.1.4. Methylphenidate

Methylphenidate acts by inhibiting the reuptake of dopamine and noradrenaline and is a central nervous system stimulant [86]. Currently, its use is only recognized for the treatment of attention deficit hyperactivity disorder.

3.1.4.1. Pathophysiological mechanisms

Methylphenidate exerts its therapeutic effects primarily by blocking the transporters responsible for the reuptake of dopamine, norepinephrine, and serotonin, thereby increasing the synaptic concentrations of these neurotransmitters [59]. Additionally, methylphenidate indirectly enhances cortical acetylcholine levels through the stimulation of cortical dopamine receptors, further contributing to its neuromodulatory effects [86].

3.1.4.2. Reported clinical improvements

In a study (n=14), a significant increase in mean GCS scores was observed following treatment, suggesting enhanced levels of consciousness [59]. Additionally, a case study employing a placebo-controlled crossover design showed that patients demonstrated increased ability to respond to verbal commands [21]. In a randomized, placebo-controlled trial in brain injury patients with acute DoC (n=50), administration of methylphenidate was associated with temporary improvements in arousal in seven patients, with three patients leading to a higher consciousness level category (although group-level effects were not statistically significant) [67].

3.1.4.3. Lack of improvement and determinant of response

A meta-analysis of single-subject repeated crossover trials assessing the effects of methylphenidate in DoC patients found no clinically meaningful improvements in responsiveness or accuracy during command-following tasks [71]. Subgroup analyses, including those focused on patients in a MCS and those without ceiling effects, also failed to demonstrate significant improvement. These findings suggest that methylphenidate may not be effective in enhancing behavioral responsiveness in this population, and that individual patient characteristics may play a key role in determining treatment response [67].

3.1.4.4. Safety profile

No adverse effects related to modafinil administration were reported in these studies [21,59,67,71]. In the context of treatments for attention deficit hyperactivity disorder, methylphenidate has been associated with several adverse effects, including modest increases in blood pressure, headaches, psychiatric adverse effects, sleep disturbances, gastrointestinal symptoms and weight loss [87].

3.1.4.5. Biomarkers

Neuroimaging findings (n=14) have identified potential biomarkers associated with the response to methylphenidate [59]. A six-week treatment with methylphenidate was linked to significantly increased cerebral glucose metabolism, particularly in the left precuneus and right posterior parietal cortex. Additional regions showing increased metabolism included the right precuneus, right superior and middle temporal gyri, and bilateral middle occipital gyri. Importantly, changes in GCS scores were positively correlated with increased glucose

metabolism in the bilateral precuneus, bilateral middle occipital gyri, and right middle frontal gyrus. These findings suggest that enhanced metabolic activity in these regions may serve as a biomarker of clinical response to methylphenidate.

3.1.5. Modafinil

Modafinil is a psychostimulant commonly prescribed for the treatment of narcolepsy, with or without cataplexy. Its pharmacological action involves the inhibition of norepinephrine and dopamine reuptake. This mechanism enhances wakefulness and alertness, making modafinil an effective agent for managing excessive daytime sleepiness associated with sleep disorders such as narcolepsy [88].

3.1.5.1. Reported clinical improvements

To our knowledge, only one study (n=24) has specifically examined the link between modafinil administration (from 100mg up to 300mg per day) and changes in levels of consciousness in DoC patients [52]. Their findings revealed a significant difference in total Wessex Head Injury Matrix (WHIM) scores between before and after treatment [52]. A notable 92% of the TBI patients showed improvement with modafinil, compared to only 50% of the non-TBI group. Moreover, seven patients progressed from an UWS to an MCS. Notably, in a subset of four patients, the authors reported full recovery of consciousness, with observed functional object use and consistent interactive communication [52].

3.1.5.2. Safety profile

No adverse effects related to modafinil administration were reported in this study (n=24)[52]. The adverse events associated with modafinil in a sample of 125 patients with multi-sclerosis included 138 total adverse events, with 40% of patients experiencing at least one adverse event[89]. The most common effects were gastrointestinal disorders (15%), nervous system disorders (18%) and psychiatric disorders (14%) [89].

3.1.6. Bromocriptine

Bromocriptine exerts its effects by directly and persistently stimulating post-synaptic dopaminergic receptors, thereby compensating for dopamine depletion [90]. Through this mechanism, it helps restore dopaminergic activity in the brain and is currently used as a therapeutic option in the treatment of Parkinson's disease.

3.1.6.1. Reported clinical improvements

Two clinical studies reported notable functional and cognitive improvements associated with bromocriptine (from 2.5 to 20 mg daily in divided doses) administration in DoC patients following TBI. In the first study, a cohort of MCS patients (n=36) showed diverse domains of recovery [60]. Accelerated arousal was observed in 47% of patients within 4 to 40 days, while 41.2% demonstrated improved Glasgow Outcome Scores (GOS 4 or 5) within 90 days.

The second study, based on TBI patients in a UWS (n=5), revealed consistent and progressive recovery across multiple outcome measures [39]. DRS scores improved at 1-, 3-, 6-, and 12-months post-injury, with patients transitioning from the UWS to moderate disability levels. CRS scores also increased, indicating enhanced alertness and cognitive awareness. Functional Independence Measure (FIM) scores also improved from complete dependence to levels ranging from minimal assistance (n=2) to full independence (n=3). These findings highlight bromocriptine's potential role in enhancing arousal, cognitive responsiveness, and functional autonomy in patients with severe brain injuries.

3.1.6.2. Safety profile

No adverse events related to bromocriptine administration were reported in these studies [39,60]. In general, Bromocriptine is generally well tolerated. A review of the available safety data indicates common side effects including headache, nausea, and nasal congestion [91]. Rare but serious adverse events such as myocardial infarction, stroke, and pulmonary fibrosis (at high doses) have been reported in an observational study [92].

3.1.7. Selegiline

Selegiline is a selective monoamine oxidase type B (MAO-B) inhibitor, primarily used in the treatment of Parkinson's disease [93]. MAO-B is an enzyme responsible for breaking down monoamines such as dopamine in the brain [93]. By degrading dopamine, MAO-B helps regulate its levels and activity. In addition to its MAO-B inhibitory action, selegiline also exerts effects by blocking the reuptake of catecholamines such as dopamine and norepinephrine, thereby enhancing their availability in the synaptic cleft.

3.1.7.1. Reported clinical improvements

To our knowledge, only one study has specifically investigated the potential clinical effects of selegiline in DoC patients [46]. In this study, patients (n=10) received selegiline for 10 weeks. Two patients fully recovered consciousness during treatment, while two patients progressed from MCS− to MCS+. These diagnostic improvements persisted during the one-month follow-up period. Three additional patients showed increased arousal without a change in clinical diagnosis, with effects similarly persisting beyond treatment cessation. Notably, one of these patients transitioned from UWS to MCS+ during treatment, with the improvement sustained one month after discontinuation. Overall, this study provides preliminary evidence of the possible benefits of selegiline on arousal and consciousness levels in patients with chronic DoC.

3.1.7.2. Lack of improvement and determinant of response

A comparison between the four patients who exhibited a change in clinical diagnosis and those who did not improve revealed no statistically significant differences in key demographic or clinical variables [46]. These included age, CRS-R score at study entry, and time since injury. No significant differences were found for gender, etiology, neuroimaging findings, or initial diagnosis [46].

3.1.7.3. Safety profile

In three cases, selegiline had to be discontinued due to adverse effects, including protracted diarrhea and supraventricular tachycardia [46].

3.2. Gamma-aminobutyric acid (GABA) agonists

3.2.1. Baclofen

Baclofen is a GABA-B receptor agonist that acts throughout the central nervous system (CNS), particularly in the cortex and thalamus, leading to the inhibition of excitatory neurotransmission [61]. It is widely used for its antispastic properties and can be administered orally or via intrathecal continuous infusion (ITB; intrathecal baclofen) when oral treatment is insufficient or poorly tolerated due to systemic side effects (see adverse effect section). ITB allows for more targeted action on the CNS, resulting in better tolerability and fewer systemic effects [94].

3.2.1.1. Pathophysiological mechanisms

Due to its enhancement of inhibitory GABAergic transmission, baclofen has demonstrated robust efficacy in the management of spasticity [94]. However, clinical observations have reported unexpected improvements in consciousness following ITB [26,53,61], suggesting that its effects may extend beyond motor control. Several mechanisms have been proposed to explain this phenomenon.

ITB may exert its effects by modulating spinal circuits, thereby influencing the transmission of afferent signals to the cortex [40]. In such individuals, impairments in sensory gating (which are the mechanisms that normally filter out irrelevant sensory, motor, and cognitive stimuli) may lead to a pathological overflow of information to higher brain regions [40]. Considering this hypothesis, by regulating spinal activity, ITB could contribute to a more effective filtering process, allowing for improved cortical function and a better chance of conscious recovery. This suggests that baclofen may indirectly improve consciousness by reducing pain and spasticity.

Margetis et al., 2013 [61] proposed a more direct mechanism for the effect of baclofen on the recovery of consciousness by its modulation of thalamocortical circuits, potentially enhancing excitatory activity within awareness-related pathways. It has been demonstrated that baclofen strongly suppresses GABA release from fast-spiking interneurons in infragranular and supragranular layers, decreasing perisomatic inhibition onto pyramidal neurons [95]. This disinhibition enhances cortical excitability in response to thalamic inputs, facilitating sensory signal transmission.

Furthermore, it has been hypothesized that the ITB plays a role in promoting serotonin release, which may also influence alertness. Indeed, the stimulation of presynaptic GABA-B receptors has been shown to facilitate serotonin release by reducing inhibitory input onto serotonergic neurons within the dorsal raphe nuclei. Furthermore, systemic administration of baclofen appears to enhance serotonin synthesis in the striatum, likely through GABA-B receptor activation in extrinsic brain regions [96].

Eventually, it has been suggested that ITB could improve axonal conduction in damaged neurons [24]. It has been showed that GABA signaling promotes axon regeneration by playing crucial role in molecular signaling pathway

[97]. Given the heterogeneity of axonal injury patterns across etiologies, understanding this mechanism could help identify which patients might benefit most from ITB.

3.2.1.2. Reported clinical improvements

Numerous reports have documented unexpected or delayed recovery of consciousness in patients with traumatic, anoxic, or hemorrhagic brain injuries following ITB therapy [28,40,53,73]. Our review includes 11 articles reporting consistent improvements in both spasticity and consciousness, regardless of the route of administration or etiology. Effective doses ranged from 50µg/day intrathecally to 2 mg/kg orally with a duration of treatment ranging from a few days to several months. The reported improvements ranged from increased alertness to full recovery of consciousness.

Several case reports have highlighted notable cognitive and motor improvements following ITB treatment [23,25–28,73]. A case study [26] described enhanced, purposeful motor responses emerging 14 months after a spontaneous brain hemorrhage, likely due to spasticity relief, though this alone may not fully explain the recovery. Similarly, Sara et al. 2007 reported regained bilateral hand movements and meaningful gestures two weeks after ITB initiation, despite only mild spasticity improvement [28]. A case series (n=2) reported that one of two patients was able to walk with a cane after six months of ITB [55], suggesting broader functional recovery.

Other reports emphasize cognitive and communicative improvements. Case studies documented full consciousness recovery within five weeks of ITB [25], as weel as vocalizations evolving into functional communication within one month[27]. After six months of treatment with 100 µg/day ITB, a case series observed improvements in all five patients [40].

However, such improvements have not been consistently replicated. Divergent outcomes have been described in two patients: one recovered attentional and memory functions, while another developed behavioral disturbance [42]. Similarly, a patient showed improved emotional and semantic responsiveness, though oral language did not recover [23].

Taken together, these findings support a potential role for baclofen in both motor recovery and the improvement of consciousness [53,94]. However, larger-scale studies are needed to identify reliable predictors of treatment and delay response, as the benefits appear to vary significantly in the absence of clearly defined predictive factors.

3.2.1.3. Lack of improvement and determinants of response

Although there is compelling evidence supporting the positive effects of baclofen, some trials have failed to demonstrate any significant clinical benefit.
In a cohort of diverse etiologies treated with ITB (n=8) [61], it has been reported that three patients showed no improvement in wakefulness (two with TBI and one with non-communicating hydrocephalus). Interestingly, time from injury to treatment initiation did not appear to significantly influence outcomes in this series. However, early intervention could theoretically yield better results.

A cohort of patients with varying etiologies and consciousness states (n=26) offered new insights [53]. They found that positive responses were more common within the first three months of ITB initiation and that these early improvements were more likely to persist over time.

3.2.1.4. Safety profile

Systemic administration of baclofen in severe spasticity often requires high doses, notably in the reports included in this review, with doses up to 150mg a day, which may increase the risk of side effects (irritability, aggressivity, auditory hallucinations, drowsiness) without ensuring therapeutic benefit [24]. ITB allows for lower doses and localized action, minimizing systemic toxicity. However, this approach is not without risks. Reported complications include infections and wound dehiscence (in 2 patients out of 8) [61], while other complications described in the literature, such as dural breaches causing cerebrospinal fluid leaks and serious withdrawal symptoms upon pump removal represent general risks associated with pump implantation [41], highlighting the importance of careful patient selection before pump implantation.

Careful and repeated assessments over time are essential to ensure optimal baclofen titration as intolerance to the treatment may present as hypotonia or lethargy [41].

3.2.1.5. Biomarkers

ITB treatment appeared to normalize sleep-wake cycles in patients, potentially supporting the recovery process [23]. Several biomarkers suggest that baclofen may improve vigilance states, including a clear distinction between wakefulness and sleep [40]. The preservation of sleep-specific EEG features (such as spindles, K-complexes, slow-wave and Rapid Eye Movement sleep patterns) and a symmetric, reactive background rhythm are associated with better prognosis. Furthermore, the integrity of hypothalamic structures, particularly the suprachiasmatic nucleus, can be inferred from the maintenance of a coherent circadian rhythm [98].

Additionally, a case study measured the baseline EEG frequency and observed an increase from 2.5–4.5 Hz pre-treatment to 6–8 Hz post-treatment, which coincided with notable behavioral improvements [28].

Clinical scales, such as the Ashworth Scale and the CRS-R, remain essential tools for monitoring spasticity reduction, improvement of consciousness and fine-tuning baclofen dosage.

3.2.2. Zolpidem

Zolpidem, a hypnotic agent of the imidazopyridine class, acts selectively on the α1 subunit of the GABA-A receptor complex. While its sedative effects in healthy individuals are well documented, paradoxical arousal responses have been reported in non-affected individuals and in patients with DoC [99]. These unexpected clinical effects have sparked growing interest in zolpidem as a potential therapeutic option for patients with severe brain injuries.

3.2.2.1. Pathophysiological mechanisms

It has been proposed that following a brain injury, the brain engages in a protective mechanism by downregulating metabolic activity in affected regions, mediated by GABAergic inhibition [31], to limit further neuronal damage but can also result in widespread cortical deactivation. Zolpidem, by modulating GABA-A receptors, can directly

inhibit GPi neurons, thereby mimicking the normal inhibitory influence of MSNs and disinhibiting the thalamus [6]. This mechanism offers a plausible explanation for the paradoxical arousal responses observed in some patients, as transient GPi inhibition may partially restore thalamocortical activity and functional connectivity.

3.2.2.2. Reported clinical improvements

Our review includes 17 articles reporting improvements in consciousness, regardless of the route of administration or etiology. Effective doses ranged from 10 to 20mg orally with a duration of treatment ranging from a single administration to several months of treatment. Two articles showed no behavioral change.

Numerous case reports [29,30,32–37,43,62,74,100] and small-scale studies [47,63] have described striking behavioral improvements following zolpidem administration in patients with DoC. These improvements include purposeful motor activity, re-emergence of speech, response to verbal commands [76-79], and even walking [35]. In some cases, these effects appeared within 20 to 30 minutes and lasted for two to four hours [77, 79, 81], often reappearing with repeated administration throughout the day [35].

While some responses were subtle, such as oriented movements [37] or eye opening [32], other cases described drastic improvements. A case study reported an emergence from a minimally conscious state within 45 minutes of a single 10 mg dose [30]. Two TBI patients fully regained consciousness after four weeks of daily zolpidem, with lasting effects post-treatment [74]. A major, though transient, recovery in a patient with eight years of akinetic mutism has been observed 20 minutes after zolpidem intake, as he regained communication, partial autonomy, and mobility, despite persistent deficits [101]. However, this paradoxical awakening was transient, typically wearing off after about two hours.

A case of recovery in a patient initially diagnosed with a UWS has been reported, as the patient transitioned to a MCS following treatment. Thonnard et al., 2013 (n=60) reported behavioral improvements in 12 patients following administration of 10 mg of zolpidem [62]. Further assessments conducted after the initial response revealed that 4 of these patients exhibited sustained functional improvements (such as the functional use of objects, intentional communication and eye opening without stimulation), yielding a responder rate of 6.7%

Similarly, a placebo-controlled study (n=84) found that only 4.8% of them were definite responders to zolpidem, with no clear demographic distinctions between responders and non-responders [102].

3.2.2.3. Lack of effect or improvement and determinants of response

Despite encouraging results in some patients, it is essential to acknowledge that zolpidem unfortunately does not lead to improvement in most cases. Table 4 summarizes the outcomes reported for zolpidem, given the highly variable and paradoxical effects observed across studies. No clinical benefits were reported in a series of eight patients with DoC [64]. However, a sample of this size may be insufficient to detect a statistically significant effect for a drug with a response rate of only 5–10%. Similarly, Singh et al., 2008 observed no significant improvement in behavioral scores following administration of 10 mg of zolpidem [31], even though other reports have documented striking positive changes.

Etiology

The underlying cause of the brain injury appears to be a major determinant of response (Table 5). Most studies

reported a beneficial effect with a daily dose of 10 mg, but a case study observed clinical improvements only with a 20 mg dose in a patient with anoxic brain injury, raising the question of dose optimization according to etiology [34].

Patients with TBI generally show a higher likelihood of responding to zolpidem. This may be due to the structural preservation of large-scale neural networks that are functionally dormant but potentially reactivatable with zolpidem [88, 89]. In contrast, a prospective study (N=31) reported that among patients who showed improvements, cerebrovascular disease was the most common etiology, suggesting variability across cohorts [9]. Notably, cases involving anoxic brain injury often show poorer responsiveness [30,35].

Pharmacological Differences

Drug response may arise from different pharmacological target. A retrospective study (n=146) compared zolpidem and lorazepam in a cohort with mixed etiologies [75]. Zolpidem selectively binds to the α1 subunit of GABA-A receptors, while lorazepam acts non-selectively on a modulatory site across various α subunits [103], potentially influencing a broader neural network. Their results showed better responses to zolpidem in TBI patients, while anoxic brain injury patients responded more to lorazepam, highlighting the importance of tailoring pharmacological strategies to the etiology.

Emergence of Drug Tolerance

Focusing specifically on zolpidem, a case study reported the development of tolerance with repeated administration. An initially strong response progressively weakened over several days, with shorter and less effective periods of improvement. After about five consecutive days, the therapeutic benefit became negligible. Attempts to increase dosing frequency failed to restore efficacy and sometimes caused sedation. A drug-free interval of two to three weeks was typically required to regain a meaningful response [101].

3.2.2.4. Safety profile

A placebo-controlled double-blind study (n=84) reported decreased arousal in two patients and shaking or restless movements in seven patients [102].

3.2.2.5. Biomarkers

EEG has also proven to be a promising predictive tool. A prospective study (n=31) found that the appearance of beta-band activity after zolpidem administration predicted improved consciousness at six months, with 92.3% specificity and a 90% positive predictive value. Calabrò et al., 2014 further supported this by demonstrating concurrent improvements in EEG voltage and amplitude (presence of theta-beta rhythm) that mirrored clinical recovery [34].

A case series studied three MCS patients using a zolpidem versus placebo trial (2 days each) [100]. After zolpidem, 18-fluorodeoxyglucose (FDG) cerebral PET imaging showed increased metabolism in the dorsolateral, mesiofrontal and prefrontal cortices (key areas involved in the mesocircuit of consciousness [6]) which was not seen with placebo. By acting on GABA-A receptors in the GPi, zolpidem inhibits its activity, helping to restore thalamic stimulation of the prefrontal cortex which helps promote cognitive recovery [6].

3.3. Other

3.3.1. Remifentanil

Remifentanil is a potent, ultra-short-acting synthetic opioid analgesic used during surgery to provide rapid and controllable pain relief, with effects that dissipate quickly after administration [53].

3.3.1.1. Pathophysiological mechanisms

Remifentanil acts as μ-opioid receptor (MOR) agonists, producing analgesic effects [105]. A potential mechanism for their impact on consciousness involves the modulation of dopaminergic activity through GABAergic disinhibition[106]. Specifically, MOR activation in the brain's reward circuitry suppresses GABAergic inhibitory transmission in the ventral tegmental area, leading to reduced inhibitory postsynaptic events. This disinhibition facilitates increased dopamine release in the striatum and prefrontal cortex, which may in turn support short improvements in consciousness after surgery.

3.3.1.2. Reported clinical improvements

One retrospective study (n=50) reviewed DoC patients who underwent surgical procedures, aiming to examine changes in their level of consciousness before and after the operation [65]. Postoperative improvements in consciousness were observed in 44% of their patients, with a significant increase in their CRS-R total scores by 1 to 4 points compared to their preoperative scores. Notably, the auditory and visual subscales demonstrated significant gains. However, the observed improvements in consciousness lasted only between 8 to 48 hours following emergence from anesthesia.

3.3.1.3. Lack of improvements and determinant of response

To better understand the factors associated with postoperative consciousness improvement, the study divided patients into two groups: those who improved after surgery and those who did not. Significant differences were observed between the two groups in terms of etiology, preoperative diagnosis, and preoperative CRS-R total and subscale scores (particularly in the auditory, visual, and motor domains) with relative factors of postoperative improvement being more favorable in patients with TBI compared to those with anoxic brain injury, and in patients in a MCS compared to those in an UWS.

Importantly, intraoperative opioid consumption (the converted morphine dose of remifentanil and sufentanil) was significantly different between the two groups, whereas no such differences were found for other anesthetic agents, surgical approaches, or anesthesia durations. Additionally, while preoperative diagnosis and etiology were linked to postoperative outcomes, the total dose of opioid analgesics administered did not significantly differ across etiologies or diagnostic categories.

3.3.1.4. Safety profile

No adverse events were reported in this study [65]. In the context of remifentanil administration for general anesthesia in healthy adults, a quantitative systematic review in 13057 patient reported that remifentanil was

associated with lower blood pressure and heart rate; however, high doses administered over a short period of time may induce thoracic rigidity [107].

3.3.2. Ketamine

Ketamine, initially developed as an anesthetic, is now increasingly recognized for its complex pharmacological profile, which includes potent antidepressant and analgesic properties [108]. While its analgesic effects have traditionally been attributed to NMDA receptor antagonism [109], growing evidence suggests the involvement of multiple additional mechanisms, positioning ketamine as a promising option, particularly in the management of pain[110].

3.3.2.1. Pathophysiological mechanisms

Complexity of the brain signal, reflecting the integration and differentiation of neural activity, is a key correlate of consciousness and is typically reduced in DoC patients[111]. Psychedelics have been shown to enhance brain complexity in healthy individuals [112], suggesting that pharmacological agents like ketamine might also modulate complexity of the brain signal in DoC patients and thereby influence consciousness-related processes [113].

3.3.2.2. Reported clinical improvements

To our knowledge, only one pilot study has investigated the effects of ketamine in DoC patients [48]. In this within-subject, placebo-controlled design, three male patients with different etiologies (TBI/subarachnoid hemorrhage/carbon monoxide intoxication) and diagnoses (UWS/MCS-/MCS+) were included. Patients appeared more aroused during ketamine sessions, spending more time with eyes open. Additionally, a reduction in spastic paresis was observed in the MCS patients after ketamine, as measured by the Modified Ashworth Scale. As the UWS patient responded to a command during the ketamine session, the patient's diagnosis improved to MCS+.

3.3.2.3. Lack of improvements and determinant of response

No consistent behavioral improvements were observed. On the contrary, a decrease in behavioral scores (Simplified Evaluation of CONsciousness scale) was reported in the two MCS patients.

3.3.2.4. Safety profile

No adverse events were reported during ketamine administration. Classical adverse effects of ketamine observed in a sample of 87 non-DoC patients included hypertension (44.8%), vomiting (28.7%), nausea (9.2%), emergence delirium (6.9%), desaturation (4.6%), and other effects such as confusion and drowsiness (4.6%) [114].

3.3.2.5. Biomarkers

Ketamine administration was associated with notable changes in EEG-based biomarkers[48]. At the spectral level, power spectra analyses revealed alterations in both aperiodic and periodic components: the aperiodic slope appeared to flatten with increasing ketamine dose, and a shift was observed in the theta band, either through

decreased power or a frequency peak shift toward faster rhythms. In terms of complexity metrics, whole-brain Lempel-Ziv complexity (LZC; a measure of signal diversity) increased at the group level during the ketamine session compared to placebo.

3.3.3. Psilocin

While psychedelics like psilocin are known to enhance brain complexity in healthy individuals, patients with DoC typically exhibit reduced neural complexity [115]. It has been proposed that increasing complexity of the brain signal through psychedelic intervention could enrich the patient's phenomenal experience and potentially expand their behavioral responses [116].

3.3.3.1. Pathophysiological mechanisms

Psilocin, a serotonergic psychedelic, has been shown to enhance synaptic plasticity by promoting dendritic growth and spine formation [117]. Psilocin acts mainly as a partial agonist at 5-HT2A receptors, whose activation in cortical areas drives its psychedelic effects [118]. Whole-brain computational models combined with deep learning evaluated the potential of various neuromodulatory systems to shift brain dynamics in DoC patients toward healthier states and found thatamong all systems, the $5HT_{2A}$ receptor (targeted by psilocin) showed the highest perturbational efficiency, highlighting psilocin as a particularly promising candidate for therapeutic intervention in DoC [119].

3.3.3.2. Reported clinical improvements

A recent case study explored the effects of psilocin, a classic psychedelic acting primarily on the serotonin $5\text{-}HT_{2A}$ receptor, on the consciousness level of a patient with a prolonged DoC [38]. Prior to administration via gastric tube (a single dose of liquid tincture psilocin, estimated 25 mg), the patient transitioned from MCS− to MCS+. Following psilocin intake, the clinical status fluctuated, dropping briefly to UWS during the EEG recording period, then returning to MCS−. Notably, despite the lack of sustained clinical improvement, spontaneous behaviors not previously observed at rest emerged after the administration of psilocin (e.g. lifting of both legs). While these behaviors were not sufficient to support a stable diagnostic change, they suggest a possible transient enhancement of behavioral responsiveness associated with psilocin.

3.3.3.3. Safety profile

This case study didn't report any major adverse events aside from a moderate, transient increase in blood pressure [38].

3.3.3.4. Biomarkers

EEG analyses showed that psilocin increased brain complexity and altered power spectra and connectivity patterns, notably with a shift toward higher-frequency activity and changes in delta and gamma bands. These results, observed without seizure activity, support the relevance of EEG-based markers to quantify and monitor the effects of psilocin in DoC patients.

4. Summary and Perspectives

This review focused on pharmacological treatments for DoC grounded in the mesocircuit model. According to this model, dopaminergic agents primarily target striatal dopamine neurons, while GABAergic agents influence GABA neurons in the GPi [6]. By modulating these key nodes, these drugs aim to restore the striato-pallido-thalamo-cortical loops, which are crucial for the maintenance and recovery of consciousness. Beyond dopaminergic and GABAergic systems, other mechanisms have been hypothesized, such as MOR-mediated disinhibition of dopaminergic neurons, as suggested by a clinical observations on remifentanil [65]. Additionally, serotonergic agents like psilocin, a 5-HT_{2A} receptor agonist, may increase the complexity of brain signal and responsiveness in DoC patients by enhancing cortical dynamics, as preliminarily observed in a single case report [38]. These interpretations require confirmation in larger, controlled studies.

Several pharmacological agents have demonstrated encouraging effects in restoring consciousness. Amantadine, the most widely studied dopaminergic agent, remains the only drug currently recommended, based on a large randomized controlled trial showing modest efficacy [120]. Other agents, including apomorphine, levodopa, bromocriptine, methylphenidate, modafinil, selegiline, zolpidem and baclofen, have shown clinical improvements in case series or small cohorts.

Despite promising preliminary data, many patients do not exhibit significant clinical improvement. The heterogeneity of DoC populations, including variability in time since injury and etiology (TBI vs. non-TBI), complicates the interpretation of treatment effects. The marked neuroanatomical variability of brain lesions across patients likely contributes to the inconsistent responsiveness observed with all pharmacological agents. While a detailed mechanistic mapping of these neuroanatomical substrates and their relationship with therapeutic target would be highly informative, it falls beyond the scope of the present review. Future dedicated work addressing this issue could help identify biomarkers predictive of treatment responsiveness and guide more personalized therapeutic interventions.

Pharmacological interventions for DoC carry risks of adverse events, which must be carefully weighed against potential benefits in these already severely disabled patients. Dopaminergic drugs can induce cardiovascular and neuropsychiatric side effects [7], while GABAergic agents may cause sedation or confusion [32]. Emerging therapies such as psychedelics require cautious monitoring given their profound effects on brain function and subjective experience [114].

Objective biomarkers are essential to monitor treatment effects and predict outcomes. Neurophysiological markers (EEG patterns, connectivity measures), neuroimaging findings (fMRI, PET), and autonomic indicators have been proposed as candidate biomarkers to assess brain network integrity and responsiveness to pharmacological agents.

4.1. Evidence Gaps and Future Directions

Current evidence suffers from a lack of robust randomized controlled trials and relies heavily on small cohorts and case reports. The complex pathophysiology of DoC and variability in assessment methodologies further challenge definitive conclusions. Additionally, heterogeneity in drug dosages, timing, and treatment durations limits comparability across studies.

By modulating neural excitability without the systemic side effects of drugs, noninvasive approaches such as transcranial direct current stimulation or repetitive Transcranial Magnetic Stimulation (rTMS) provide a promising

complementary or alternative avenue for promoting recovery in this population [121]. Future research should leverage advanced methodologies such as artificial intelligence and in silico modeling [119] to predict drug efficacy, find new potentially beneficials therapeutics or neurophysiological targets [122], or personalize treatment [123]. Integration of multimodal biomarkers, large-scale databases, and computational tools could accelerate discovery and optimize pharmacological strategies for DoC. Collaborative efforts are essential to design rigorous trials that address current gaps and translate promising candidates into clinical practice.

5. Conclusion

In this narrative review, we summarized the pharmacological interventions proposed to promote recovery of consciousness disorders, including dopaminergic agents (such as amantadine, apomorphine, and levodopa), GABA agonists (including zolpidem and baclofen), as well as serotonergic agents and psychedelic compounds. We discussed their underlying pathophysiological mechanisms, reported clinical improvements, lack of efficacy in some cases, determinants of response, safety profiles, and potential biomarkers. The 67 studies provide a comprehensive overview of the current evidence. However, this field still lacks large-scale randomized controlled trials. Future research should aim to better control for key variables such as time since injury and etiology, which are essential for interpreting treatment outcomes and identifying reliable predictors of recovery.

Declarations

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Conflicts of Interest

The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval

Not applicable, as this is a narrative review and does not involve human participants or animals.

Consent to Participate

Not applicable.

Consent to Publish

All authors consent to the publication of this manuscript.

Availability of Data and Material

Not applicable.

Code Availability

Not applicable.

Author Contribution Declaration

AG performed the literature review, paper selection and extracted the data, interpreted the findings, and drafted the manuscript.

CG contributed to paper selection and data extraction and participated in writing the manuscript.

MMV contributed to the data extraction, interpretation of findings and manuscript preparation.

NL conceived and supervised the project, defined the scope and structure of the review, contributed to data extraction and manuscript preparation.

All authors critically revised the manuscript for intellectual content, contributed to the final version of the manuscript, approved its submission and agree to be accountable for the work.

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Table 1. Findings of the literature review for dopaminergic agents (number of patients, etiology, evaluation method, diagnosis at baseline, drug(s) used and dosage, treatment effect)

Author(s), Year	N	Etiology	Evaluation method	Diagnosis at baseline	Drug(s) and dosage	Treatment effect
Lee et al. (2020) [49]	84 (retrospective)	Hemorrhagic stroke (n=36), ischemic stroke (n= 23), TBI (n=17), anoxia (n=5), other (n=3)	CRS-R	UWS (n=21), MCS- (n=39), MCS+ (n=24)	Amantadine: from 100mg twice a day, to 200 twice a day; Cerebrolysine: 2,125g/10ml IV 2x/d	Patients in the dual regimen group had greater increases in CRS-R scores than those in the single regimen group.
Alkhachroum et al. (2020) [54]	44 (retrospective)	TBI and non TBI	EEG before and after amantadine	Not mentioned.	Amantadine (100mg) twice daily	Age and cumulative amantadine dose were independently linked to recovery of command following, while EEG sleep features and the emergence of a posterior dominant rhythm (PDR) after treatment correlated with recovery, but increases in PDR frequency did not predict consciousness recovery.
Keller & Mueller (2007) [56]	18 (prospective open-labelled study)	TBI or hypoxia	EEG		Amantadine (100mg), L-dopa (100mg) and Amphetamine (10mg)	EEG data showed no differences between patients treated with stimulating drugs and those untreated, while skin conductance and electromyogram activity were higher in treated patients across conditions, but heart rate differences were not statistically significant.
Bender Pape et al. (2020) [45]	4 (pilot trial)	TBI	DOCS25	Not specified.	Amantadine (2x100mg) + rTMS; 300 trains of pairs 100µs pulses - 100ms interpulse and 5s intertrain)	Meaningful gains in DOCS25 for 75% of treatment segments + auditory-language gains after rTMS
Gatto et al. (2024) [68]	37 (randomized controlled trial)	SAH	GCS, CRS-R, GOS	GCS between 3 and 11	Amantadine 100 mg tablets once a day and placebo in the control group, with doses progressively increased, until 200 mg tablets twice a day.	No significant neurological improvement either during the weeks of intervention or after 3 or 6 months.
Zafonte et al. (1998) [13]	1 (case report)	TBI	CNC	CNC score severe category (average 3,42)	Amantadine 100mg/d, with 100mg increase every 5 days to a maximum of 400mg/day	The patient's clinical and functional status improved in parallel with increased amantadine dosage, with sustained recovery.
Lehnerer et al. (2017) [14]	1 (case report)	SAH	CRS-R	UWS	Amantadine 100mg/day up to 300mg/day (100mg increase per day)	After 16 days, the patient improved from 5/23 to 23/23 at CRS-R. Was able to communicate with a speaking valve. Could move each limb on demand.

Schnakers et al. (2008) [15]	1 (case report)	Anoxia	CRS-R	MCS	Amantadine 200mg	CRS-R scores increased during the first treatment period, with motor function improving after 1 week and auditory function after 3 weeks, while no substantial improvements were seen during the second treatment period.
Vargus-Adams et al. (2010) [69]	7 (randomized controlled trial)	TBI (n=5), anoxic (n=1), stroke (n=1)	CRS-R	UWS (n=5), MCS (n=2)	Amantadine 4 mg/kg/day for 7 days followed by 6 mg/kg/day for 14 days	No significant correlation was found between average drug concentration and recovery on the CRS-R, but the two patients with the highest amantadine levels showed the most favorable recovery.
Giacino et al. (2012) [66]	184 (randomized controlled trial)	TBI	CRS-R, DRS	UWS, MCS	Amantadine, from 100 mg twice per day, to 200 mg twice per day at week 4	Both groups (placebo versus amantadine) had significant improvement in the DRS score over the 4-week treatment interval, but the amantadine group had significantly faster recover.
Avecillas-Chasín & Barcia (2014) [16]	1 (case report)	Non TBI	Not mentioned	MCS	Amantadine, from 100mg b.i.d. twice a day to 150mg b.i.d. twice a day.	By the third day: regained command following, visual pursuit, and object manipulation; communication and recognition abilities emerged by day 14.
Chen et al. (2019) [17]	1 (case report)	TBI	GCS	UWS, GCS=6	Amantadine, from 100mg twice a day to 200mg twice a day.	The patient's post-treatment GCS was 8, and the patient tracked both sound and visual cues.
Gao et al. (2020) [50]	46 (retrospective)	Cerebral hemorrhage	GOS	UWS	Amantadine, from 100mg twice per day to 200 mg twice per day.	Among 46 patients, 12 received oral amantadine, with 50% regaining consciousness within 3 months but remaining severely disabled (GOS 3), while the other 6 remained in UWS (GOS 2).
Gao et al. (2020) [76]	7 (prospective open-label study)	Cerebral hemorrhage	CRS-R	UWS	Amantadine, from 100mg twice per day, to a maximum dose of 200mg.	All patients showed consciousness improvement, with five achieving significant CRS-R score increases and regaining consciousness after 12 weeks despite residual impairments.
Giacino & Troot. (2004) [18]	1 (case report)	TBI	CRS	Coma	Amantadine, from 100mg/day to (400mg/day) + bromocriptine (10mg/day)	Patient showed automatic motor responses, recovery of visual pursuit, reproducible command-following, intelligible verbalization
Estraneo et al. (2015) [19]	1 (case report)	TBI	CRS-R	MCS+	Amantadine, started at 50 mg b.i.d. and increased to 100mg.	CRS-R scores improved significantly within 3 days, with the patient able to communicate and use two objects. There was a dose-dependent effect.
Blum et al. (2025) [51]	442 (retrospective)	Non-TBI	GCS	Not specified.	Amantadine, from 200mg twice a day to 400mg twice a day.	267 patients were classified as responders (GCS improved by ≥ 3 points within 5 days), with lower mortality at discharge and follow-up.
Fridman eat al. (2010) [57]	8 (prospective open-label study)	TBI	CNC, DRS	UWS (n=6), MCS (n=2)	Apomorphine (from 2mg/h for 12 hours to 8mg/h 12–16 hours per day).	All patients regained command following and CNC at 0 within one year. Some regained walking abilities

Fridman et al. (2009) [12]	1 (case report)	TBI	CNC, DRS and GOS Extended	MCS	Apomorphine for 12 hours/day, using a dose escalation infusion rate from 2mgh to 8mgh	The patient showed rapid improvement in motor and cognitive function, with some decline upon its initial discontinuation on day 84 leading to resumption; after continued treatment until day 179, apomorphine was stopped, followed by a brief motor regression resolved with l-dopa, after which the patient fully recovered normal professional and daily functioning without stimulants.
Sanz et al. (2024) [7]	13 (prospective open-label study)	TBI (n=4) ; Non-TBI (n=2)	CRS-R	UWS (n= 1), MCS- (n=3), MCS+ (n=2)	Apomorphine - 1758mg total dose (in 30 days) max 6mg/h at maintenance rate	Significant behavioral and diagnostic improvements, increased CRS-R scores, increased alpha-band connectivity, and a 13.8% rise in whole-brain metabolism.
Ugoya & Akinyemi (2010) [55]	11 (prospective case series)	TBI	Following commands.	UWS	L-dopa/carbidopa (initiation at 100mg, daily increase until 375mg)	Improvement in the state of consciousness was noted in most patients (82%).
Matsuda et al. (2005) [44]	5 (case reports)	Not specified.		UWS (n=4) and MCS (n=1)	Levodopa 100mg	Recovery from UWS or MCS in 4 days to 1.5 months.
Bancalari et al. (2018) [20]	1 (case report)	SAH (n=1) (left PICA aneurysm rupture)	CRS-R	MCS+	Levodopa/carbidopa 100/25 3x/day	8 days after treatment onset, intelligible speech (CRS-R = 14/23).
Krimchansky et al. (2004) [58]	8 (prospective open-label study)	TBI	Following commands.	UWS	Carbidopa 25mg/levodopa 250mg Seven patients started with 25% of a tablet three times daily and one patient with 25% of a tablet twice daily. The dosage was gradually increased by a quarter of a tablet every 7 days on average. The maximum dosage reached (only one patient) was three tablets a day.	Progressive behavioral improvements, with seven out of eight patients regaining reciprocal interaction after an average of 31 days, while one patient showed limited response, remaining in a minimally conscious state at discharge.
Matsuda et al. (2003) [70]	2 (case reports)	TBI		UWS	Patient 1: Levodopa (450 mg a day), Levodopa/benserazide (100/25mg) three times a day Patient 2: Levodopa/carbidopa (100/10mg) three times a day	After Levodopa, the patient's rigidity was reduced and his eyes began to follow moving objects. After Levodopa/benserazide, he began to respond by blinking. Patient 2: the patient's akinesia and rigidity were reduced and he was able to obey simple command
Kim et al. (2009) [59]	14 (prospective open-label study)	TBI and non TBI	GCS	GCS mean score=7.79	Methylphenidate (0.3 MG/kg), twice daily	A significant improvement was observed in mean GCS scores.

Othman et al. (2025) [67]	50 (randomized controlled trial)	Non-TBI (n=48) ; TBI (n=2)	FOUR, SECONDs	Coma (n=7), UWS (n=21), MCS- (n=17), MCS+ (n=5)	20 mg Methylphenidate (20mg) ; Apomorphine (2mg) ; placebo (saline solution)	Clinically improved arousal was observed after 7 methylphenidate, 4 apomorphine, and 1 placebo dose. Transient changes to higher consciousness levels occurred after 3 methylphenidate, 4 apomorphine and 1 placebo dose.
Martin & Whyte (2007) [71]	22 (meta-analysis of n-of-1 studies)	TBI and non TBI	DRS, CRS-R		Methylphenidate (mean dose=13.3, +/- 4.6)	No significant drug effect was found on responsiveness or accuracy in dual-response command protocols, though scores under both drug conditions were correlated, while MPH showed small to medium negative effects on responsiveness and accuracy in single-response protocols.
Piguet et al. (1999) [21]	1 (case report)	TBI	No validated scale	FIM score of 18.	Methylphenidate in a double-blind placebo-controlled design ([A-B]-[C-B]-A-B]-[C-B].	Significant improvement in the frequency of responses to verbal commands compared to placebo.
Gatto et al. (2023) [72]	3 (case reports)	TBI	MAS, GMFM	UWS	hr-NGF administration, at a total dose of 50 gamma/kg	PET and Single Photon Emission Computed Tomography revealed increased tracer uptake in specific brain areas, EEG showed improved cerebral activity, and the patient improved by 3 points on the scale, transitioning from an UWS to severe disability with notable cognitive gains.
Dhamapurkar et al. (2017) [52]	24 (retrospective)	12 TBI, 12 non TBI	CRS-R, WHIM	Not specified.	Modafinil, dosage gradually increased from 100mg up to 300mg daily.	17 of the 24 patients had higher WHIM scores when on Modafinil.
Chiaretti & al. (2017) [22]	1 (case report)	TBI	CRSHC-scale, House-Brackmann, Sunnybrook Facial grading scale, Range of Head Movements	UWS	NGF 0.1 mg/kg	Significant cognitive improvements in communication, attention, and verbal comprehension were observed after the first intranasal NGF cycle.
Munakomi et al. (2017) [60]	36 (prospective open-label study)	Diffuse axonal injury, contusions, hypoxic brain injury	GOS, BMC	MCS	Bomocriptine, from 2.5 to 20 mg daily in divided doses.	41.2% showed improved GOS; hemiparesis improved by at least 1 BMC score in 55.6%; aphasia improved in 80%; moderate cognitive improvement was seen in 66.7%; and memory improvement was observed in 50%.
Passler & Riggs (2001) [39]	5 (case reports)	TBI	DRS, CRS and Barry Rehabilitation Inpatient	UWS	Bromocriptine, from 1.25mg twice per day, to 2.5mg twice per day.	All 5 patients demonstrated improvement in their level of cognitive and physical functioning

			Screening of Cognition.			
Masotta et al. (2018) [46]	7 (pilot trial)	Not specified.	CRS-R	UWS, MCS- and MCS+	Selegiline (5mg/day for a week, 10mg/day for 9 weeks)	Selegiline treatment led to clinical and arousal improvements in several patients, especially with vascular etiology, with benefits persisting up to one month after treatment.

BMC = British Medical Council ; CNC = Coma Near-Coma scale ; CRSHC = Clinical Rating Scale for Head Control; CRS-R = Coma Recovery Scale – Revised; DOCS25 = Disorders of Consciousness Scale 25 ; DRS = Disability Rating Scale ; EEG = Electroencephalography ; FIM = Functional Independence Measure; FOUR = Full Outline of UnResponsiveness; GCS = Glasgow Coma Scale ; GMFM = Gross Motor Function Measure; GOS = Glasgow Outcome Scale ; GOS-E = Glasgow Outcome Scale – Extended; MAS = Modified Ashworth Scale ; MCS- = Minimally conscious state minus; MCS+ = Minimally conscious state plus; N/A = Not applicable; NGF = Nerve Growth Factor ; PET = Positron Emission Tomography ; PICA = Posterior Inferior Cerebellar Artery; rTMS = Repetitive transcranial magnetic stimulation ; SAH = Subarachnoid Hemorrhage; SECONDs = Simplified Evaluation of CONsciousness Disorders; TBI = Traumatic Brain Injury; UWS : Vegetative State / Unresponsive Wakefulness Syndrome; WHIM : Wessex Head Injury Matrix.

Table 2. Findings of the literature review for Gamma-aminobutyric acid (GABA) agonists (number of patients, etiology, evaluation method, diagnosis at baseline, drug(s) used and dosage, treatment effect)

Author(s), Year	**N**	**Etiology**	**Evaluation method**	**Diagnosis at baseline**	**Drug(s) and dosage**	**Treatment effect**
Halbmayer et al. (2022) [53]	26 (retrospective)	TBI (n=19), anoxic (n=2), SAH (n=3), intracerebral hemorrage (n=2)	CRS-R, MAS	UWS (19), MCS (7)	Baclofen (from 130µg to 1100µg)	In 26 patients treated with ITB for severe supraspinal spasticity, the greatest improvements in CRS-R and MAS scores occurred at 3 months post-implantation, with smaller CRS-R gains and no further MAS decline after 6 months.
Formica et al. (2017) [23]	1 (case report)	Pilocytic astrocytoma	LOCFAS, CNC, DRS	UWS	Baclofen (2 mg/kg/d), delorazepam (0.5 mg/d), melatonin up to 1 mg/d, fluoxetine 20 mg/d, modafinil (100 mg bid)	Following modafinil treatment, the patient showed recovery of wakefulness and awareness, emotional responsiveness, oral feeding, and non-verbal communication abilities, with final assessments indicating improved functional status (LOCFAS 3, CNCS 0).
Taira & Hori (2006) [73]	1 (case report)	TBI	Not specified	UWS	Baclofen (no posology mentioned)	The patient started talking and eating by himself. Six months later, he returned home on foot.
Sarà et al. (2009) [40]	5 (case reports)	Hemorrhage (2), anoxic (1), TBI (2)	MAS, DRS, CRS-R	UWS	Baclofen 100µg	CRS-R scores increased after 2 weeks, followed by variable behavioral responsiveness improvements in each patient, leading to differing degrees of functional score upgrades by the end of follow-up.
Shrestha et al. (2011) [25]	1 (case report)	TBI	Not specified.	UWS	Baclofen 50µg every day for 2 weeks and then 100µg	The patient's limbs became less stiff. His higher mental function also showed signs of improvement. Occasionally, he also started showing his emotions.
Oyama et al. (2010) [41]	2 (case reports)	SAH	MAS	Command following /no command following	Baclofen 50-100µg/day	Could eat, wash, write/could follow command eat communicate, walk with cane
Margetis et al. (2014) [61]	8 (prospective open-label study)	TBI (n=6), anoxic (n=1), Healthy control (n=1)	MAS, CRS-R	UWS, MCS	Baclofen 50–150µg	All patients improved spasticity, but only Patient 8 showed a notable consciousness improvement, with CRS-R increasing from 11 to 22 about two years post-ITB.
Formisano et al. (2019) [26]	1 (case report)	Intracranial hemorrhage	NCS-R, CRS-R	UWS	Baclofen 60µg	Behavioral responsiveness dramatically improved, with CRS-R increasing from 6 to 12, marked by intentional motor responses in the left limbs and recovery of functional communication.

Lanzillo et al. (2016) [27]	1 (case report)	TBI	DRS, CRS-R	Not specified.	Baclofen 75µg/day, pregabalin 150mg/day, atenolol 100mg/day / Baclofen 500µg / Ziconotide 1.178microg/day-2.39microg/day + baclofen 500-590µg	Patient regained ability in: oral feeding, vocalization, later could form words and answer questions
Sarà et al. (2007) [28]	1 (case report)	SAH	No scale	UWS	Baclofen infusion ; start at 100µg/day then increased to 200 and 300µg/day	The patient exhibited behavioral and cognitive recovery, including purposeful motor actions and verbal communication.
Al-Kohdairy et al. (2015) [42]	2 (case reports)	TBI	GCS, CRS	MCS	Baclofen, from 38 µg to 45mg.	Rapid emergence from MCS was accompanied by reduced spasticity, improved behavior and communication, and after 6–7 months, the patient returned home communicating via letters or computer and regained oral communication with full sentences.
Taira (2009) [24]	2 (case reports)	TBI	Not specified.	UWS	Patient 1: Baclofen 50mg/day for the initial, 3 days, and subsequently 75mg/day for l0 day and 100mg/day for l0 days Patient 2: Baclofen 50mg/day for 5 days, 100mg/day and the injection was continued for 23 days	Patient 1 began spontaneous eye-opening 3 days after starting baclofen, spoke some words by day 5, responded to verbal commands by day 8, and was able to sit up by day 14; he was an ordinary schoolboy with normal development. Patient 2: by day 5, he responded vaguely to verbal commands and slowly opened and closed his eyes; after five 100 mg injections, he began spontaneous eye opening, and by day 18, he could extend his fingers on command and eat orally.
Spiegel et al. (2023) [29]	1 (case report)	Anti-NMDA encephalitis	CRS-R	MCS	Zolpidem - 5mg from day 25 to day 27 then 4x5mg until day 33	CRS-R = 15 at baseline, CRS-R = 23 at day 8
Thonnard et al. (2013) [62]	60 (prospective open-label study)	TBI and non TBI	CRS-R	UWS/MCS	Zolpidem (10mg)	At the group level, zolpidem intake did not change diagnoses or CRS-R total and subscores, but individually, 12 patients showed behavioral improvements or increased CRS-R scores after zolpidem.
Zhou et al. (2024) [74]	2 (cases report)	TBI	CRS-R	eMCS	Zolpidem (10mg)	Both patients retrieved intelligible verbalization for the first time an hour after Zolpidem intake.
Shames & Ring (2008) [30]	1 (case report)	Hypoxia		MCS	Zolpidem (10mg)	After 45 minutes, the patient's condition dramatically improved, emerging from MCS.
Whyte et al. (2014) [102]	83 (placebo-controlled, double-blind trial)		DRS and CRS-R		Zolpidem (10mg)	The incidence of definite zolpidem response is 4.8%. In general, the magnitude of the drug effect is already diminished or absent an hour after it was first seen.

Singh et al. (2008) [31]	1 (case report)	TBI	Had to select common objects, soccer teams and coloured objects by following a series of instructions.	MCS	Zolpidem (10mg)	Average scores were not better on treatment. His scores off medication were significantly better for 2 of the tests.
Rodriguez-Rojas et al. (2013) [32]	1 (case report)	TBI	CRS-R	UWS	Zolpidem (10mg)	After administration, patient changed from her usual sleep-like state and started to open and close her eyes, together with non-stereotyped limb movements and startle reactions.
Chatelle et al. (2014) [100]	3 (case reports)	Hypoxia	CRS-R	MCS+ / MCS- / MCS+	Zolpidem (10mg) in a randomized order, in a double blind 2-way design.	All three patients consistently followed simple commands, recognized and appropriately used objects, and communicated functionally.
Bomalaski & Smith (2017) [33]	1 (case report)	TBI	DRS and GCS	MCS	Zolpidem (10mg) twice (2 days apart)	After the first administration, the patient quickly became more interactive with improved motor function and functional object use; the second administration led to initial decline followed by significant improvements in arousal, communication, and motor function at 2 hours, returning to near baseline by 4 hours.
Calabrò et al. (2015) [34]	1 (case report)	Hypoxia	CRS-R and prolonged EEG.	UWS	Zolpidem (20mg/day), with an increase of 5mg/week	Significant improvement in awareness and wakefulness was observed at a 20mg dose, accompanied by increased EEG amplitude and theta rhythm in the right temporo-occipital region, with a CRS-R score of 13.
Zhang et al. (2021) [75]	146 (retrospective)	TBI (n=87), hemorrhagic stroke (n=11), anoxic (n=48)	CRS-R	UWS (n=63), MCS (n=74), eMCS (n=9)	Zolpidem (max 2x15mg) / Lorazepam (1-10mg/day max) / None + Amantadine (max 2x200mg)	The overall positive rate was 11.6% (11/95), among which the positive rate for the zolpidem trial was 6.3% (5/79) and for the lorazepam trial was 14.0% (6/43; $p > 0.05$).
Clauss & Nell (2006) [43]	3 (case reports)	TBI-TBI-Anoxia	GCS	UWS	Zolpidem 10mg	Meaningful behavioral improvements in all three patients, including enhanced interaction, emotional responsiveness, communication, and goal-directed actions, with GCS scores increasing from 6–9 at baseline to 10–15 post-treatment.
Gao et al. (2023) [9]	31 (prospective open-label study)	Anoxia, TBI, cerebrovascular disease and metabolic encephalopathy	EEG, CRS-R	UWS/MCS	Zolpidem 10mg	58.1% of patients showed improved consciousness; the presence of beta bands post-zolpidem predicted improved consciousness with high specificity and positive predictive value.

Whyte & Myers (2009) [47]	10 (pilot trial)	Not specified.	CRS-R	UWS, MCS	Zolpidem 10mg	1 patient showed a clear difference in performance 30min after administration
Cohen & Duong (2008) [35]	1 (case report)	Anoxic	Not specified.	Not specified.	Zolpidem 10mg	Increased arousal began within an hour of medication, lasting about 3 hours, and further improved with dose escalation over 3 weeks, leading to increased speech, social interaction, assisted walking, and willingness to eat, allowing resumption of daily therapy activities including walking.
Delargy et al. (2019) [36]	1 (case report)	SAH	CRS-R, WHIM, MATADOC	MCS	Zolpidem 10mg (+ interdisciplinary team rehabilitation)	Following Zolpidem administration and an 8 week intervention, the patient showed transient verbal responsiveness and sustained improvements in communication and function, with CRS-R scores increasing to 23.
Khalili et al. (2020) [63]	12 (prospective open-label study)	TBI	GCS motor score	UWS	Zolpidem 10mg 2x/day	Significant improvement in motor scores, but no significant differences between responders and non-responders based on age, disease duration, or baseline motor function.
Machado et al. (2011) [37]	1 (case report)	Ischemic stroke	No validated scale	UWS	Zolpidem 10mg, single dose - 1 healthy control	Clear behavioral signs of arousal alongside autonomic changes, with an initial parasympathetic response followed by marked sympathetic activation, coinciding with yawning and reduced heart rate variability.
Hao et al. (2022) [64]	8 (prospective open-label study)	Not mentioned.	EEG, CRS-R	Not mentioned.	Zolpidem (no posology mentioned).	All eight patients did not show any clinical improvement. The global relative theta power showed a significant reduction at the group level.

CNC = Coma Near-Coma scale ; CRS-R = Coma Recovery Scale – Revised; DRS = Disability Rating Scale ; EEG = Electroencephalography ; eMCS= emergence from the minimally conscious state; GCS = Glasgow Coma Scale ; LOCFAS = Level of Cognitive Functions Assessment Scale ; MAS = Modified Ashworth Scale ; MATADOC = Music Therapy Assessment Tool for Awareness in Disorders of Consciousness; MCS- = Minimally conscious state minus; MCS+ = Minimally conscious state plus; N/A = Not applicable; NCS-R = Nociception Coma Scale – Revised ; NMDA = Anti-N-methyl-D-aspartate; SAH = Subarachnoid Hemorrhage; TBI = Traumatic Brain Injury; UWS : Vegetative State / Unresponsive Wakefulness Syndrome; WHIM : Wessex Head Injury Matrix.

Table 3. Findings of the literature review for other pharmaceutical agents (number of patients, etiology, evaluation method, diagnosis at baseline, drug(s) used and dosage, treatment effect)

Author(s), Year	**N**	**Etiology**	**Evaluation method**	**Diagnosis at baseline**	**Drug(s) and dosage**	**Treatment effect**
Ge et al. (2023) [65]	50 (prospective open-label study)	TBI (n=18), intracranial hemorrhage (n=16), anoxic (n=16)	CRS-R	UWS, MCS	All patients received surgical treatments under general anesthesia, including percutaneous SCS (n = 35), SCS (n = 11), cranioplasty (n = 5), ventriculoperitoneal shunt (n = 4), and skin dilator implantation (n = 1). The surgical methods were summarized into minimally invasive operations (n = 30) and open operations (n = 20).	Postoperative consciousness improvement was found in 44% of the patients. The postoperative CRS-R scores of these patients significantly increased by 1–4 points compared with their preoperative scores.
Cardone et al. (2025) [48]	3 (pilot trial)	TBI, SAH, carbon monoxide intoxication	CRS-R, EEG, MAS	UWS, MCS-, MCS+	Ketamine, from 0.15 μg mL-1, to 0.75μg mL-1.	During ketamine infusion, there was an increase in brain complexity for the three patients, but there was no positive change in their diagnosis. As time spent with eyes open increased, patients exhibited reduced spastic paresis and increased arousal.
Cardone et al. (2025) [38]	1 (case report)	TBI	SECONDs, NCR-R, EEG	MCS+	Psilocin: 2.5 g liquid tincture (estimate psilocin: 25 mg)	After psilocin intake, the patient showed transient unresponsiveness followed by new motor behavior. EEG revealed increased complexity, higher-frequency power, and inverse power-connectivity changes.

CRS-R = Coma Recovery Scale – Revised; EEG = Electroencephalography ; MAS = Modified Ashworth Scale ; MCS- = Minimally conscious state minus; MCS+ = Minimally conscious state plus; NCS-R = Nociception Coma Scale – Revised ; SAH = Subarachnoid Hemorrhage; SCS = Spinal Cord Stimulation; SECONDs = Simplified Evaluation of CONsciousness Disorders; TBI = Traumatic Brain Injury; UWS : Vegetative State / Unresponsive Wakefulness Syndrome.

Table 4. *Zolpidem responders and non-responders across all included articles. Percentage of patients who responded to zolpidem treatment, categorized by study and by etiology.*

Authors	N	Etiology	Subgroup responders (n)	Subgroup responders (%)
Zhang et al. (2021) [75]	146 (n=90 for zolpidem)	TBI (n=49)	5	10.2%
		ABI (n=30)	0	0%
		Hemorrhage (n=11)	0	0%
Khalili et al. (2020) [63]	12	TBI	6	50%
Gao et al. (2023) [9]	31	TBI (n=8)	5	62.5%
		ABI (n=15)	5	33.3%
		Cerebrovascular (n=7)	7	100%
		Metabolic encephalopathy (n=1)	1	100%
Hao et al. (2022) [64]	9	TBI (n=3)	2	66.7%
		ABI (n=2)	1	50%
		Stroke (n=4)	1	25%
Thonnard et al. (2013) [62]	60	TBI (n=31)	8	13.3%
		ABI (n=18)	2	3.3%
		Stroke (n=6)	1	1.7%
		Metabolic encephalopathy (n=2)	1	1.7%
		Mixed etiologies (n=3)	0	0%
Whyte et al. (2014) [102]	79	TBI (n=56)	7	12.5%
		ABI (n=9)	1	11.1%
		Ischemic (n=14)	0	0%
Whyte & Myers (2009) [47]	15	TBI (n=8)	1	12.5%
		ABI (n=5)	0	0%
		Toxic encephalopathy (n=1)	0	0%
		Stroke (n=1)	0	0%

ABI = Anoxic Brain Injury; TBI = Traumatic Brain Injury

Table 5. *Overall percentage of responders to zolpidem across all etiologies combined, as well as stratified by etiology, based on the selected articles.*

	All etiologies	TBI	ABI	Cerebrovascular	Encephalopathy	Others
Total cases	296	167	79	43	4	3
Responders	54	34	9	9	2	0
% of response	18.24%	20.35%	11.39%	20.93%	50%	0%

ABI = Anoxic Brain Injury; TBI = Traumatic Brain Injury. The proportion of responders per category was calculated by dividing the number of responder patients by the total number of patients in the corresponding category to obtain the corresponding percentages.

Fig. 1 *The fronto-parietal mesocircuit model. The red arrows indicate inhibitory connections within the mesocircuit model, while the green arrows represent excitatory connections. The thickness of each arrow reflects the strength of the effect. On the left, a healthy brain. On the right, following brain injury: the model proposes that damage to the central thalamus, through loss of input and neuronal degeneration, disrupts excitatory signals to medium spiny neurons in the striatum. Without this excitatory drive, the striatal inhibition of the internal globus pallidus (GPi) is weakened, allowing the GPi to maintain strong inhibitory output toward its targets, most notably the already hypoactive central thalamus. This cascade contributes to further suppression of thalamic function and reduced thalamocortical communication.* Created in https://BioRender.com