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Amantadine, Apomorphine and Zolpidem in the Treatment of Disorders of Consciousness

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Abstract: Survivors of severe brain injuries may end up in a state of 'wakeful unresponsiveness' or in a minimally conscious state. Pharmacological treatments of patients with disorders of consciousness aim to improve arousal levels and recovery of consciousness. We here provide a systematic overview of the therapeutic effects of amantadine, apomorphine and zolpidem in patients recovering from coma. Evidence from clinical trials using these commonly prescribed pharmacological agents suggests positive changes in the neurological status in patients, leading sometimes to dramatic improvements. These findings are discussed in the context of current hypotheses of these agents' therapeutic mechanisms on cerebral function. In order to enhance our understanding of the underlying pathophysiological mechanisms of these drugs, we suggest combining sensitive and specific behavioral tools with neuroimaging and electrophysiological measures in large randomized, double-blind, placebo-controlled experimental designs. We conclude that the pharmacokinetics and pharmacodynamics of amantadine, apomorphine and zolpidem need further exploration to determine which treatment would provide a better neurological outcome regarding the patient's etiology, diagnosis, time since injury and overall condition.

Keywords: Amantadine, apomorphine, zolpidem, disorders of consciousness, unresponsive/vegetative state, minimally conscious state, pharmacological treatments, mechanism of action.

INTRODUCTION

Following severe brain damage, pharmacological agents can be given to counteract disturbances of specific neurotransmitter systems. The type of etiology may guide the choice of treatment since each type of injury can lead to different outcomes in brain function. In fact, traumatic brain injury (TBI) is associated with a cascade of primary and secondary deleterious effects (*e.g.*, ischemia, hypoxia, excitotoxicity, cerebral edema) on brain structures and neurotransmitters. TBI is also associated with an increase in excitatory neurotransmitters, such as aspartate and glutamate, and a decrease of dopamine levels [1, 2]. This loss of dopamine is suggested to be a consequence of diffuse axonal injury leading to white matter degeneration in prefrontal, dorsolateral brainstem and other brain areas [3, 4]. Therefore, dopamine agonists are often used to treat TBI patients [5, 6]. Anoxic brain injuries also have damaging effects on the neurochemical system. Like TBI, anoxic accidents have been reported to cause a rise in glutamate levels. However, unlike TBI, the post-anoxic brain is associated with higher concentrations of dopamine and gamma-aminobutyric acid (GABA) [1], and the lesions will primarily affect watershed regions (*e.g.*, hippocampus, basal ganglia, striatum) [7]. Pharmacological agents are often used in the acute phase to stabilize vital signs but also to induce neuroprotective effects such as preventing excitotoxic cell death (with the administration of progesterone) and cerebral edema (with citicoline) [8].

Severe brain injury can lead to coma where patients remain with their eyes closed and do not respond to external stimulation [9]. When patients open their eyes but remain unconscious they are diagnosed as being in a *vegetative state,* or now, preferably referred to as the *unresponsive wakefulness syndrome* (VS/UWS) [10, 11]. Patients who evolve from that condition show non-reflexive, goal-directed behaviors (*e.g.,* visual pursuit and reproducible responses to commands), and hence are considered to be in a *minimally conscious state* (MCS). MCS patients demonstrate partially preserved fluctuating levels of awareness but they remain unable to functionally communicate. Depending on the complexity of the demonstrated behaviors, it was recently proposed that MCS patients can be subcategorized into MCS- (*i.e.,* when only showing simple non-reflex movements, such as visual pursuit, orientation to pain or non-contingent behaviors) and MCS+ (*i.e.,* when patients recover the ability to respond to simple commands) [12, 13]. Once these patients can communicate in a functional manner and/or show functional object use, they are diagnosed as having emerged from MCS [14].

These patients with disorders of consciousness (DOC) represent an important proportion of the disabled population worldwide. Although our understanding of the neurophysiological and neurochemical correlates of consciousness has greatly evolved over the past decades, routine care has not yielded specific, evidence-based medical treatments for patients with DOC. Treatment to promote the emergence of consciousness will most often be administered in the subacute (1 to 3 months post-insult) and the chronic (3 months post-anoxic injuries and 12 months post-traumatic injuries) phases. Frequently prescribed pharmacological treatment include dopaminergic agents (*e.g.*, amantadine, apomorphine, methylphenidate, levodopa, bromocriptine) and GABAergic agents (*e.g.*, zolpidem, baclofen) [8]. Although all these drugs have been previously reported to have positive neurological effects, this article will mainly focus on the amantadine, apomorphine and zolpidem treatments, which are to date among the most commonly prescribed and studied in patients with DOC.

Assessing Consciousness

In order to efficiently evaluate the effects of a given pharmacological treatment, the assessment of the patients' level of consciousness is of paramount importance. Currently, behavioral assessment is considered to be the "gold standard" for detecting signs of consciousness at the bedside [15]. Many different scales have been developed to assess patients who are recovering from coma,

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and this last decade has particularly focused on the differential diagnosis between VS/UWS and MCS. Providing accurate diagnosis through the use of specialized scales allows for optimal clinical management (i.e., rehabilitation needs, pharmacological treatment, end-of-life decisions). Table **1** gives a non-exhaustive overview of the behavioral scales used to assess patients recovering from coma.

Consciousness can be grossly divided in two major components that are assessed separately at the patient's bedside: arousal and awareness (Fig. **1**) [16]. Arousal (or wakefulness) is determined by opening of the eyes and is seen as a prerequisite for higher-level brain functioning. From a neurochemical point of view, it is mediated by a complex network encompassing cholinergic reticulothalamic projections, glutaminergic thalamocortical projections, and reticulocortical projections (a network of dopaminergic, noradrenergic, serotonergic, and cholinergic projections) [17, 18]. Awareness, on the other hand, involves the activity of a widespread thalamo-cortical and fronto-parietal network. Behaviorally, it can be inferred from following commands or non-reflex behaviors [19]. The phenomenological complexity of the awareness component can be further divided into two dimensions: external and internal awareness [20]. External awareness refers to the conscious perception of one's environment through the sensory modalities (*e.g.,* visual, auditory, somesthetic, or olfactory perception) and is associated with the activation of dorsolateral prefrontal cortices and posterior parietal cortices (regions in red, Fig. **1**). Internal awareness refers to mental processes that do not require the mediation of external stimuli or sensory input (*e.g.,* mind wandering, daydreaming, inner speech, or mental imagery) and is associated with activity related to midline posterior cingulate cortices/precuneus and anterior cingulate/medial prefrontal cortices (regions in blue, Fig. **1**) [21]. Knowing this distinction, behavioral assessment of awareness in patients with DOC mainly refers to the evaluation of external awareness, as they are unable to communicate their internal thoughts.

Assessing the Beneficial Effect of Treatment

To construct a framework for clinical decisions-making concerning treatment options, objective measures are needed to reflect the evidence from research. The use of sensitive standardized scales (*e.g.,* the Coma Recovery Scale-Revised – CRS-R) should be the primary measure to take into account when assessing the behavioral effect of the drug. The severity of the potential side effects should also be acknowledged in order to drive the choice of a therapeutic treatment. In this regard, we used the Common Terminology Criteria for Adverse Events [22] that classifies the severity of adverse events between grade 1 (mild; asymptomatic or mild symptoms, clinical observations with no medical intervention required), grade 2 (moderate; minimal, local or noninvasive intervention indicated), grade 3 (severe; medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated, disabling), grade 4 (life-threatening consequences; urgent intervention indicated) and grade 5 (death related to adverse event). Evaluation of the quality of research is also of paramount importance and this can be done with the Levels of Evidence from the Oxford Centre for Evidence-Based Medicine [23]. Level 1 includes systematic reviews (which will not be included in this article as we focus on original data), level 2 comprises randomized controlled trials, level 3 concerns non-randomized controlled cohort or follow-up studies, level 4 refers to case-series or case-control studies, and level 5 relates to mechanism-based reasoning. These three measures (behavioral tool, severity of side effect and level of evidence) will help us to evaluate the effect of amantadine, apomorphine and zolpidem treatment in patients with DOC.

The CRS-R (in b[illegible]has been shown to be the most accurate and sensitive scale in differentiating unresponsive from minimally conscious patients [36, 37]. The Functional Independence Measure (FIM) and the Mini-Mental State Examination (MMSE) are occasionally used in some of the mentioned studies but they are not included in the table because those have been developed to assess higher level of cognitive disabilities. Abl[illegible]tions: ICU=intensive care unit, VS/UWS=vegetative state/u[illegible]ponsive wakefulness syndrome, MCS=minimally conscious state, LIS=locked-in syndrome.

AMANTADINE

Amantadine increases dopamine availability in the synapse by inhibiting its reuptake and by stimulating the activation of dopaminergic receptors [38]. It has also been suggested to have an antagonist action on the N-methyl-D-aspartate (NMDA) receptors. In the 1960's, amantadine was found to have therapeutic effects

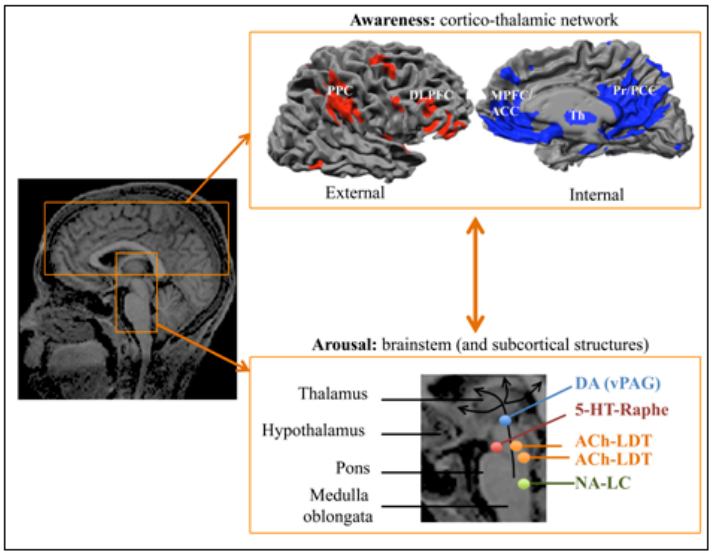

Fig. (1). Simplified illustration of the arousal and awareness systems. The ascending arousal system within the brainstem encompasses dopaminergic (DA), noradrenergic (NA), serotonergic (5-HT) and cholinergic (ACh) projections (vPAG: ventral periaqueductal grey; LDT: laterodorsal tegmental nucleus; PPT: pedunculopontine nucleus; LC: locus coeruleus). Awareness involves the mesio-prefrontal cortex (MPFC), dorsolateral prefrontal (DLPFC), anterior cingulated cortex (ACC), thalamus (Th) and posterior parietal cortex (PCC) (here shown for the right hemisphere, lateral and medial regions). Adapted with permission from [20].

Table 1. Behavioral scales used in pharmacological trials with post-comatose patients.

Authors (year) [reference]	Scale's name (abbreviation)	Specificity (average execution time in minutes)	Behavioral content (Nb of subscale and nb of items)	Scoring for response	Total score and diagnosis
Teasdale & Jennett (1974) [24]	Glasgow Coma Scale (GCS)	ICU (10)	Eye, verbal, motor (3 and 15)	Varies per item, 4–6 anchored responses	Total score 3-15 3=deep coma or death, 15=fully awake person
Born *et al.* (1988) [25]	Glasgow-Liege Scale (GLS)	ICU (10)	Eye, verbal, motor, brainstem reflexes (4 and 4)	Varies per item, 4–6 anchored responses	Total score 3=deep coma or death, 20=fully awake person
Wijdicks *et al.* (2005) [26]	Full Outline of UnResponsiveness S (FOUR)	ICU, differentiation between VS/UWS, MCS and LIS (10)	Eye response, motor response, respiration, brainstem reflexes (4 and 4)	5 anchored responses	Total score Diagnosis based on the presence or absence of operationally-defined behavioral responses to specific sensory stimulations
Rappaport *et al.* (1982) [27]	Disability Rating Scale (DRS)	Rehabilitation, moderate and severe TBI, outcome (10)	Arousal, cognition, self-care activities, level of dependence, psychosocial availability (4 and 8)	Varies per item, 4–5 anchored responses	Total score 0-29 0=no disability, 1=mild. 2-3=partial. 4-6=moderate. 7-11=moderately severe, 12-16=severe, 17-21=extremely severe, 22-24=vegetative state, 25- 29=extreme vegetative state
Rappaport *et al.* (2000) [28]	Coma/Near-Coma Scale (CNC)	Expansion of the upper range of the DRS (≥21) (10)	Visual, auditory, command following, threat response, olfactory, tactile, pain, vocalization (8 and 11)	"Occurs 2–3 times", "occurs 1–2 times" or "does not occur"	Total score 0-44 Average item score: 0.00–0.89=no coma, 0.90–2.00=near coma, 2.01–2.89 =moderate coma, 2.90–3.49=marked coma, 3.50–4.00=extreme coma
Ansell & Keenan (1989) [29]	Western Neuro Sensory Stimulation Profile (WNSSP)	Rehabilitation, post-comatose state (45)	Auditory comprehension and visual comprehension, visual tracking, object manipulation, arousal/attention, tactile/olfactory (6 and 32)	Varies per items, 3-6 anchored responses	Total score 0-110 maximal Scores between 40 and 50 are generally required for eligibility for rehabilitation. The higher the score, the better.
Gill-Thwaites *et al.* (2004) [30]	Sensory Modality Assessment and Rehabilitation Technique (SMART)	Rehabilitation, differentiation between VS/UWS and MCS (60)	Auditory, visual, tactile, olfactory, gustatory, and motor functions, wakefulness, communication (8 and 8)	5 anchored responses	Each scale score 1=no response, 2=reflex response, 3=withdrawal response, 4=localizing response, 5=differentiating response. MCS or higher if rated a score of 5 on at least one sensory modality on 5 consecutive administrations
Shiel *et al.* (2000) [31]	Wessex Head Injury Matrix (WHIM)	Rehabilitation, subtle changes in MCS (30 to 120)	Basic behaviors, social/communication, attention/cognitive, orientation/memory (62 items)	"Absent" or "present"	Total score 1=vegetative state, 62=emerging from post-traumatic amnesia

(Table 1) Co

Authors (year) [reference]	Scale's name (abbreviation)	Specificity (average execution time in minutes)	Behavioral content (Nb of subscale and nb of items)	Scoring for response	Total score and diagnosis
Hagen *et al.* (1987) [32]	Levels of Cognitive Functioning - Rancho Los Amigos (RLA)	Post-comatose state, outcome (30)	Auditory, visual, motor and oral functions, communication, memory, reasoning, orientation, arousal (8 subscales)	"Absent" or "present"	Total score 1-8 I=no response, II=generalized response, III=localized response, IV=confused/agitated, V=confused/inappropriate, VI=confused/appropriate, VII=automatic/appropriate, VIII=purposeful/appropriate
Gia[illegible] *al.* (2004) [33]	Coma Recovery Scale-Revised (CRS-R)	Differentiation between VS/UWS and MCS (25)	Auditory, visual, motor, oral, communication, arousal (6 and 23)	"Absent" or "present" (must be reproducible) Varies per item (*e.g.*, at least 3 out of 4 times)	Total score 0-23 0=coma; 23=emergence from MCS. VS/UWS, MCS and emergence of MCS diagnosis based on the presence or absence of operationally-defined behavioral responses to specific sensory stimulations (*e.g.,* MCS if visual pursuit, responses to command)
Jennett & Bond (1975) [34]	Glasgow Outcome Scale (GOS)	Outcome (5)	Level of global outcome	"Absent" or "present"	Total score 1-5 1=dead, 2=vegetative state, 3=severe disability, 4=moderate disability, 5=good recovery
Jennett *et al.* (1981) [35]	Glasgow Outcome Scale Extended (GOS-E)	Outcome (5 to 25)	Level of global outcome including measures of consciousness, level of dependence, work, social network, epilepsy (8 and 19)	"Yes" or "no" and the possibility of 3 anchored responses for some items	Total score 1-8 1=dead, 2=vegetative state, 3=lower severe disability, 4=upper severe disability, 5=lower moderate disability, 6=upper moderate disability, 7=lower good recovery, 8=upper good recovery

against influenza and it has then been prescribed as a flu treatment [39]. However, due to the frequent mutations of the virus and to the advent of new drugs, it is no longer recommended as an antiviral drug (37). The half-life of amantadine is approximately 15 hours in young patients and 29 hours in the elderly [40, 41]. In the late 1960's, a patient with Parkinson's disease reported experiencing less rigidity, akinesia, and tremor while treating a flu infection with amantadine. Interestingly, after stopping the treatment the patient observed that the Parkinson's symptoms had worsened [42]. This serendipitous case led to the development of a new treatment for Parkinson's disease [43-45]. Indeed, amantadine has been shown to be safe over a long period of time either in monotherapy or in combination with levodopa and/or anticholinergic drugs. The treatment has also been reported to have more beneficial effects during the early stages of Parkinson's with a positive impact on patients' alertness, motivation and mood [42]. Thus, it is nowadays mainly prescribed for early symptomatic treatment in order to delay the administration of levodopa [46] and is also indicated for the treatment of dyskinetic patients [47]. Amantadine has also been used to reduce agitation and to promote recovery of consciousness in post-comatose patients [48, 49]. It is usually administered orally but most of the times through feeding tubes in patients with DOC.

First Clinical Trials in Patients with Acquired Brain Injuries

In 1988, Chandler *et al.* used amantadine for the first time in two acute TBI patients recovering from coma who exhibited aggressive and agitated behaviors [49]. These behaviors substantially decreased right after the initiation of the treatment. A year later, the same team published positive results showing reduced experienced tiredness as well as lower distraction and aggressiveness in a cohort of 30 subacute and chronic TBI patients. From the cohort, 14 patients were referred to as being "unequivocal responders", and five responded favorably but presented with important side effects such as irritability, rigidity and seizures [50]. Subsequently, a third clinical trial with amantadine published in 1994 recruited 12 TBI patients with "high agitation" (n=3) or "low arousal" (n=9). After the beginning of the treatment, 10 patients had improved in terms of cognitive and/or physical functioning; two patients showed a dramatic decrease in prior agitation, and eight out of nine "low-arousal" patients displayed an increased level of responsiveness. Side effects of amantadine were reported in five patients and included pedal oedema (grade 1), hypomania (grade 3), generalized seizure (grade 2), and visual hallucinations (grade 1-2) [51].

These early clinical trials with amantadine suggest positive therapeutic effects on cognitive function, arousal level and agitation in patients with TBI. However, these studies were solely based on physicians' observations, and none of them employed standardized measures or a placebo group to control for spontaneous recovery and outcome. Moreover, the studies reviewed above were conducted before the nosology of "vegetative state" and "minimally conscious state" was clearly differentiated (as well as in some of the studies mentioned in the following sections), and hence the diagnosis might have lacked in precision (*e.g.*, low arousal). Such work

had, nevertheless, encouraged for further clinical replication in order to evaluate the potentially beneficial effects in the treatment of patients with DOC.

The Stimulating Effects of Amantadine Described with Standardized Outcome Measures

By the beginning of the 21st century, studies started to use standardized outcome measures to assess the neurorecovery effect of amantadine after acquired brain injury. For instance, a retrospective study using the Glasgow Coma Scale in 74 patients with extensive brain damage showed that the treated patients obtained higher scores than the control group receiving no treatment when discharged from the intensive care unit. The death rate was also significantly lower in the treatment group (6%) as compared to the control group (51%) [52]. The first successful double-blind placebo control randomized trial was conducted by an American team in 2002 on 35 acute TBI patients. During a six-week amantadine treatment, patients showed a higher functional improvement as assessed with the Mini-Mental State Examination [53], the Glasgow Outcome Scale, the Disability Rating Scale (DRS) and the Functional Independence Measure [54] when compared to their placebo performances [55]. Similarly, Whyte *et al*. showed that TBI patients receiving amantadine had better DRS scores four months post-injury than to those who did not received the treatment [56]. A case study by Zafonte *et al*. reported a positive response of amantadine in a MCS patient examined five months post-TBI [57]. Within the first week of treatment, the patient recovered communication capacities and showed improvement when assessed with the Coma/Near-Coma scale (CNC). Since he reached the maximal possible score at the CNC assessments after a month, the dose was then decreased. The diminution of amantadine administration resulted in a sharp worsening of CNC scores but when the administration went back to previous dosages, the patient was able to communicate again, and his CNC score increased. This case represents a good example of a dose-dependent effect of amantadine.

The clinical trials presented above reported the stimulating effects of amantadine in patients with acquired brain injuries. However, they do not provide information on patients with a slower recovery process or chronic DOC as the patients included in these four studies were in the subacute phase of their recovery. Depending on the study, the given dosage varied between 100 and 400 mg daily in adult (average of 200 mg a day) and was usually less in children (Table **2**).

Amantadine Treatment in Pediatric Populations with Disorders of Consciousness

Amantadine has also been observed to induce positive effects in the recovery process of pediatric populations. Patrick *et al*. reported the case of a patient who was in an allegedly VS/UWS for more than four months post-TBI [58]. Within the first week of amantadine treatment, he became more alert showing yes/no head nods and inconsistent command following. After an increase in amantadine dosage during the course of his treatment, he continued to make improvements, such as the pronunciation of single words and the demonstration of a sense of humor and more smiling. He also reached the maximum score at the Western Neurosensory Screening Examination scale. Upon family's request, the treatment was discontinued approximately a year and a half post-injury. This resulted in a downturn in his motor status and initiation, speech articulation, swallowing, mental alertness, as well as in his ability to maintain social interactions. The medication was then resumed at previous levels and the patient consequently regained his abilities in all behavioral areas. The same authors later reported significant improvements in 10 severely brain-damaged "low responsiveness" children after an eight-week treatment with either amantadine (n=6) or pramipexol (n=4; another agonist of dopamine) more than a one month post-injury [59]. These observations were correlated with an increased score at several behavioral scales evaluations (CNC, DRS and Western Neuro Sensory Stimulation Profile). No unexpected or significant side effects were observed in any of the cases. In a further double-blind placebo-controlled study, improvements in consciousness were observed by the treating physician when amantadine was administered to five VS/UWS and two MCS children with TBI and non-TBI etiologies. However, the changes in the CNC and CRS-R scores did not reach statistical significance at the group level [60]. A more favorable recovery slope was nevertheless observed individually in two children assessed with the CNC and in four children assessed with the CRS-R. In this study, the best clinical responses were followed with an adverse event (*i.e.,* vomiting – grade 1/2) in a child who received the highest dosage (>1.5mg/L from blood concentration sample) [61]. Given this result and previous reported dose-dependent effects of amantadine, consideration should be given to higher doses in the cases of non-responders (aside from being vigilant regarding the side effects).

No Positive Effects

Amantadine treatment has also been reported to have no effect on the patients' evolution and/or to lead to negative results. The first prospective randomized double-blind placebo-controlled study was conducted in 1999 in a rehabilitation unit. Ten conscious post-comatose TBI patients participated in this clinical trial consisting of a two-week trial of amantadine with placebo control, followed by a two-week washout and ended with a two-week of the alternative (placebo or amantadine) [62]. Although the patients generally improved during the trial, no significant differences were observed when comparing patients who had received amantadine versus placebo according to their neuropsychological outcome. The authors, however, emphasized several factors limiting the power and the generalizability of their results, such as the small sample size, the heterogeneity of their population and the acute time course. In 2000, a single case study reported no positive changes in the general condition of a subacute 9-year-old boy in VS/UWS following a near-drowning incident. Moreover, negative side effects could even be observed since the patient started to exhibit signs of autonomic instability (*e.g.,* agitation, diaphoresis, hypertension – grade 2/3) after the beginning of the treatment one month post-insult [58]. Finally, another study described the ineffectiveness of amantadine treatment (± 6 weeks post-injury) in a large cohort of 123 traumatic patients considered in a coma [63]. In the 28 cases receiving amantadine, 13 (46%) emerged from their coma (*i.e*., Rancho Los Amigos scale score; RLA ≥ 5) compared to 36 (38%) in the 95 control cases who did not receive the treatment. However, some limits could be identified in this study like the retrospective design, the lack of terminology, the sample size bias as well as a selection and treatment biases (*e.g*., the prolonged coma was the cause for the amantadine prescription) meaning that the two groups might not have been truly comparable. These methodological issues highlight the need of prospective and controlled settings in future investigations.

Etiology and Amantadine Treatment

Most of the aforementioned studies involved patients with TBI and despite some negative results they suggest that amantadine therapy generally induces behavioral and cognitive improvements (Table **2**). Recently, a study by Giacino and Whyte *et al*. confirmed these findings in a well-designed controlled study in which they assessed 184 patients who were either in VS/UWS or MCS one to four months after TBI [64]. Patients from 11 rehabilitation centers in three different countries were randomly assigned to receive amantadine or placebo treatment for one month, and were followed for two weeks after the treatment was discontinued. In keeping with evidence from the rate of change during inpatient rehabilitation (*i.e.,* due to spontaneous recovery and/or stimulation programs), both groups had improved during the one-month period. Nonetheless, functional recovery (*i.e.,* functionally meaningful

behaviors, such as consistent response to commands, intelligible verbalization, reliable yes-no communication, and functional use of objects) was significantly faster in the amantadine group than in the placebo group, as measured by the improved DRS scores. No difference was observed between patients in VS/UWS and MCS patients. Yet, there was a difference depending on the time since injury (*i.e.,* patients who were enrolled later after their injury responded better to amantadine than those who were enrolled earlier). Although improvements were generally maintained in the amantadine group after the washout period, the rate of functional recovery attenuated substantially after stopping the treatment, as previously observed in other trials. DRS scores were largely indistinguishable between the amantadine and placebo groups at the six-week follow-up assessment. Exposure to amantadine did not increase the risk of adverse events (including seizure). Taken together, these results suggest that amantadine accelerated the pace of functional recovery during active treatment in TBI patients with DOC when assessed in the acute and subacute settings.

Regarding non-TBI etiologies, another recent retrospective study explored the effect of amantadine and methylphenidate in a population of patients resuscitated after a cardiac arrest who underwent therapeutic hypothermia [65]. Out of a cohort of 588 patients, between 4 and 35 days after resuscitation, 16 patients started receiving amantadine, methylphenidate or a combination of both. Compared to the control group, patients receiving neurostimulants trended toward an increased frequency of goal-directed behaviors at the bedside (*i.e*., command following) with an improved distribution of Cerebral Performance Category scale and modified Rankin scale scores. Moreover, these patients showed a higher survival rate after hospital discharge. These preliminary results indicate a potential therapeutic option for post-cardiac arrest patients in acute settings. However, this study does not permit to isolate the beneficial effects of the therapy since some acute patients might well have recovered spontaneously. Therefore, a controlled prospective trial is still needed to fully determine the effect of amantadine in pathologies other than TBI, and to compare more closely the influence of TBI and non-TBI etiology within the same clinical trial.

Neuroimaging

To date, only two studies also used electrophysiology or neuroimaging techniques to gather objective information about the treatment efficacy and action mechanisms at the brain level. The remaining studies have solely relied on behavioral measurements to identify the effects of amantadine treatment in patients with DOC (Table **2**). The first one, published in 1990, used electroencephalogram (EEG) and showed an increase of alpha activity and a decrease in theta activity in one patient in VS/UWS who clinically responded to amantadine [66]. The second study conducted by Schnakers *et al.* in 2008 used an ABAB experimental design and fluorodeoxyglucose-positron emission tomography (FDG-PET) in a MCS patient two years after anoxic injury [67]. Neuroimaging data showed a significant amantadine-related increases in metabolic activity in the fronto-parietal network (known to be essential for the emergence of consciousness [68]) and in sensorimotor areas. These regions were previously hypometabolic when compared to healthy subjects' scans, and showed metabolic increase after 5 weeks of treatment, decrease after withdrawal and resume near-normal values after amantadine reintroduction. Behaviorally, CRS-R total score improved compared to baseline evaluations. Before the treatment, the patient only demonstrated visual pursuit as a sign of consciousness but after its initiation, he was able to follow commands and demonstrated consistent automatic motor responses (*i.e.,* mouth opening following the presentation of a spoon). During the washout period, a decline in motor activity was recorded by an actimeter (*i.e.*, a wrist-mounted device used to record the frequency and amplitude of motor activity) although the patient could still respond to commands and did not demonstrate significant CRS-R performances discrepancies.

Altogether, these studies suggest that amantadine is a suitable medication to promote recovery of consciousness in patients with DOC. Besides its neurorecovery properties amantadine has a quick onset of action with functional results observed within the first four weeks of administration. A few side effects have been reported so far, ranging from mild to severe (grade 1 to 3). It seems to be efficient in both patients in VS/UWS and MCS, and in TBI and non-TBI etiologies. Nevertheless, the rate of responders remains to be determined by directly comparing etiologies and with the utilization of appropriate standardized tools to assess the level of consciousness (*i.e.,* CRS-R). More technically advanced studies including techniques such as high-density EEG, functional magnetic resonance imaging and transcranial magnetic stimulation combined with EEG are needed to better understand the underlying mechanisms of the positive effect of amantadine in patients with DOC.

APOMORPHINE

Apomorphine is a non-selective dopamine agonist which activates D1-like and D2-like receptors as well as serotonin and α-adrenergic receptors [69]. Crossing the blood-brain barrier, this dopaminergic agent has a very rapid onset of action and a brief duration of action (*i.e.,* half-life ranging from 30 to 90 minutes after a single administration) [70]. Apomorphine can be administered orally, sublingually, nasally or rectally in single doses but it can also be administrated subcutaneously or intravenously via continuous or repeated infusions. Continuous subcutaneous administration through an external pump is preferably used for a rapid and complete absorption [71]. Intravenous administration should be avoided since crystallization of the molecule can occur, contributing to increased risks of thrombosis and pulmonary embolism. Oral administration is also not recommended because of the drug's first-pass hepatic metabolism and its poor bioavailability [69].

A Historical View

The pharmacological properties of apomorphine have been known since the end of the 19th century and the drug has since been used extensively by veterinary specialists to treat various forms of involuntary movements in farmyard animals [69]. The first descriptions of apomorphine use in humans concerned its emetic effects [72, 73]. It was employed for the treatment of various addictions such as alcohol, nicotine or heroin. Indeed, apomorphine administration can induce nausea and it was used to provoke vomiting in alcoholic patients [74] and to promote the development of Pavlovian conditioned avoidance reflexes in smokers [75]. Other psychiatric and neurological disorders such as insomnia, depression, schizophrenia, hysteria, epilepsy and erectile dysfunction were also treated using apomorphine [69, 74]. More importantly, this drug was the first dopamine receptor agonist prescribed for the treatment of Parkinson's disease [74], but the drawback of oral administration (including adverse effects and short duration of action) precluded further developments, and led to its replacement with levodopa. In the 1980's, the introduction of alternative ways of administration bypassing the first-pass effect (*e.g.*, subcutaneous or sublingual) as well as the discovery of domperidone (*i.e.,* an extracerebral inhibitor of dopamine receptors blocking the emetic side effects of apomorphine) provoked a renewed interest in the drug, and promoted the exploration of further therapeutic and diagnostic applications [74, 76].

Current Use of Apomorphine

In humans, apomorphine is mainly used for the treatment of persistent and disabling motor fluctuations in patients with advanced Parkinsonism. The standard pharmacological therapy for Parkinson's disease remains the administration of levodopa but this drug has the disadvantage of inducing "on-off" fluctuations, as well as motor and cognitive symptoms [77]. To counteract these unwanted symptoms, subcutaneous apomorphine infusion can be administered to reverse the "off" episodes within minutes of onset

[78]. Furthermore, a recent case report has highlighted the potential benefits in palliative care settings for the relief of symptoms in the terminal care of a Parkinson's disease patient [79]. Adverse side effects have been reported in patients treated with apomorphine, and these range between mild and moderate (grades 1-2), including emesis, nausea, dyskinesia, dizziness, somnolence, hallucinations, excessive yawning as well as bruises, abscesses, and necroses at the injection site [80, 81]. A recent study also reported the case of an attempted suicide in a Parkinson's disease patient who was under a high dosage of dopaminergic agents including apomorphine [82]. A recent animal study also described the beneficial effects of apomorphine on short-term memory function, suggesting a possible avenue for the treatment of Alzheimer's disease [83]. Apomorphine delivered in the form of a nasal-spray is also prescribed for the clinical management of erectile dysfunction although it does not represent a first-option treatment for this disorder [84, 85]. Last but not least, the drug's potential neurorecovery properties in severely brain-injured patients in an altered state of consciousness have been investigated for therapeutic functional outcome.

Apomorphine Treatment in Patients with Disorders of Consciousness

Only two studies, conducted in Argentina, have used apomorphine treatment in patients with DOC to promote their functional recovery [86, 87] (Table **2**). In the first study, a prospective open-label clinical trial, Fridman *et al.* described the fast recovery of a MCS patient after receiving subcutaneous intermittent continuous treatment of apomorphine [86]. The patient, who suffered from a severe TBI after a motor vehicle accident, had previously failed to respond to other pharmacological therapies such as methylphenidate and bromocriptine. Neurological examination prior to his apomorphine administrations showed spontaneous eye opening, visual pursuit and inconsistent motor responses to verbal commands. The patient was neither able to verbalize nor to use objects purposefully. He also showed severe generalized spasticity without extrapyramidal signs. The patient received apomorphine 15 weeks post-TBI, diluted to a concentration of 5 mg ml^{-1} with isotonic saline via an external pump for 12 hours per day followed by a 12-hour rest period (to mimic the diurnal cycle) for a period of 11 weeks. Just a few hours after apomorphine delivery, the patient began to move his legs systematically at request. The following day, he could move other limbs on command and he could correctly answer yes/no questions. A few days later, he was also able to name objects correctly. His behavioral and cognitive improvements were also observed on different assessments with the CNC, the DRS and the Glasgow Outcome Scale-Extended. Few mildly uncomfortable side effects were reported during the first two weeks of treatment, including sporadic penile erections, focal dyskinesias and one nocturnal hallucinatory episode (grade 1). Apomorphine was inadvertently discontinued during one afternoon, which resulted in a loss of cognitive and motor abilities that further recovered once the pump was restarted. Similarly, at the end of the treatment window, there was a slight decrease in motor function that was resolved by a one-month levodopa treatment. The patient was able to walk independently six months after the treatment and recovered normal function in daily living (as an anecdote he could play polo two years after his accident). Diffusion tensor imaging performed two years after the introduction of the treatment objectified a decrease in thalamo-cortical and cortico-thalamic projections as compared to healthy control subjects. Despite these reductions in white matter tracts, the fractional anisotropy (*i.e.,* a neuroimaging measure that reflects the quality of the remaining projections) was within normal range suggesting long-term neuronal plasticity reorganization.

In their second prospective open-label study, Fridman *et al.* included eight patients with DOC one to four months following a severe TBI (six in VS/UWS and two in MCS) from two different centers in Argentina and Israel. All except one patient underwent previous unsuccessful dopaminergic treatment (*i.e.,* levodopa, bromocriptine, amantadine and methylphenidate). Two days prior to the start of apomorphine delivery, all patients received a single dose of domperidone to avoid emetic effects. Apomorphine was here again diluted and administered using an external continuous subcutaneous infusion pump for 12 to 16 hours per day. Treatment continued for approximately three months, and in some cases up to six months. All patients responded to commands after the onset of apomorphine treatment, four patients within 10 days and the remaining others after one month. One patient died during the trial, but the cause of death was unrelated to the drug's mechanisms of action. The other seven patients showed complete recovery of consciousness with a rapid change within the first two weeks. Progressive and linear improvements in the CNC and DRS scores were described and reached normal values one year post-treatment. These ameliorations lasted even after the discontinuation of the apomorphine administrations. Out of the treatment, two patients regained full independence, two reached independent walking abilities, and the three others returned home with moderate assistance in daily living activities. Reported main side effects attributable to apomorphine were nausea, emesis, skin inflammation and nodules, dyskinesia, drowsiness, sleeping disturbances, and agitation (grade 1-2).

These two studies showed that all investigated patients completely recovered consciousness, and this functional recovery was maintained even after discontinuation of the treatment (except in the patient who died seven weeks post-treatment from an unrelated complication). One should however note that the design used in these studies does not allow the differentiation between improvements induced by apomorphine with the ones that could have occurred due to a spontaneous recovery process. More studies in VS/UWS and MCS patients are needed to confirm these results using a double-blind placebo-controlled design as well as neuroimaging techniques.

POTENTIAL MECHANISMS EXPLAINING THE POSITIVE EFFECTS OF DOPAMINERGIC AGENTS

Clinical observations have shown that the use of dopamine agents such as amantadine and apomorphine facilitates functional rehabilitation, and hence neuronal plasticity. The mechanisms of action still remain unclear but hypotheses have been suggested to explain the favorable effect of dopaminergic agents on arousal and awareness in patients with DOC. The neurobehavioral effects may reflect enhanced neurotransmission in the dopamine-dependent nigrostriatal, mesolimbic, mesocortical and/or thalamic pathways (Fig. **2**) [59, 88, 89]. These pathways mainly originate in the brainstem and project forward to interact with different structures of the midbrain and cerebral cortex. The nigrostriatal pathway, which starts in the substantia nigra and terminates in the basal ganglia or striatum, plays a role in behavior initiation and motor functions, and is known for its involvement in Parkinson's disease. The mesolimbic pathway, which projects from the midbrain ventral tegmental area to the nucleus accumbens in the ventral striatum, is associated with emotional processes, motivation, learning, and memory. The mesocortical circuit, encompassing excitatory projections from the ventral tegmental area to the prefrontal cortex, is believed to be involved in cognition and executive function (via the dorsolateral prefrontal cortex) as well as in emotions and affect (via the ventromedial parts of the prefrontal cortex) [89]. In addition to these three pathways, another system including the thalamus is important for mediating arousal and awareness, and hence might play a key role in the functional recovery of severe brain-injured patients. In this thalamic pathway, dopamine exerts effects on the thalamus and the basal ganglia, which then connects to the supplementary and primary motor areas, the dorsolateral prefrontal cortex and the limbic structures (*i.e.,* nucleus accumbens) [90].

Dopaminergic agents have thus been suggested to increase thalamic tonus firing via the striato-thalamic projections [91]. Accord-

Table 2. Studies using amantadine or apomorphine treatment in post-comatose patients.

Study Author (year) [reference]	Design	Level of evidence	N patients (etiology)	Diagnosis	Time since injury	Treatment procedure	Results	Effect
Amantadine								
Chandler *et al.* (1988) [49]	Case series	4	2 (TBI)	Agitated	±4 and 16 months	Increasing dose up to 400 mg daily until at least discharge	Resolution of agitated and violent behavior, cooperation	+
Gualtieri *et al.* (1989) [50]	Cohort study	4	30 (TBI)	Moderate to severe lesion (14 > RLA VI and 16 RLA III-V)	2 months to 12 years	50-100 mg daily, ↑ 50-100 mg/week during 6 weeks up to 1 year. If no response, stop treatment after 6 weeks	14 "unequivocal responders" and 5 "responded favorably": ↑ awakening, ↓ tiredness, distractedness and aggressiveness	None and +
Horiguchi *et al.* (1990) [66]	Case study	4	1 (progressive degeneration)	VS/UWS	3 years	Increasing dose from 150 mg to 300 mg daily for 2 weeks then 300 mg daily for 4 weeks	Responses to command, visual pursuit, verbalizations. EEG: ↑ alpha activity, ↓ theta activity	+
Nickels *et al.* (1994) [51]	Retrospective case series	4	12 (9 TBI)	9 "low arousal" and 3 "high agitation"	1.5 to 9 months	Increase dose from 50 mg up to 200 mg daily for 6 days up to 1.5 month	2 ↓ agitation, 8 ↑ responsiveness: ↑ focused and sustained attention, arousal, psychomotor speed, vocalization, mobility, participation in therapy, ↓ tiredness, anxiety	None and +
Zafonte *et al.* (1998) [57]	Case study	4	1 (TBI)	MCS (average CNC score of 3.42, eyes tracking)	5 months	4 months treatment. Start with 100 mg/day, ↑100 mg/5days with maximum 400 mg/day. After 35 days, diminution 100 mg/5days. When 100 mg/day, ↑ again to 400 mg/day	Emergence from MCS, ↓ CNC score (reached 0), active participation. Dose-dependent effect	+
Schneider *et al.* (1999) [62]	Prospective, randomized, double-blind, placebo-control, crossover	2	10 (TBI)	Conscious post-comatose (deficits in attention)	(Sub)acute – rehabilitation phase	2-week amantadine or placebo treatment, 2-week washout, 2-week alternative treatment. 50 mg twice daily increased every 3 days to a maximum of 150 mg twice daily	No improvement as assessed by standardized neuropsychological testings and the Neuro- behavioral Rating Scale	None
Patrick *et al.* (2000) [58]	Case study	4	2 (1 TBI, 1 anoxia)**	2 "complicated emergence from coma" (DRS >18; RLA II-III)	1 and 4 months	TBI: 100 mg twice a day for >1 year; anoxia: 50 mg/day for 2 days then 50 mg twice a day for 5 days	TBI: more alert, yes/no head nods, command following, verbalization. ↑WNSE, RLA and ↓ DRS Anoxia: no improvement and sympathetic storms	+ and -
Meythaler *et al.* (2002) [55]	Prospective, randomized, double-blind, placebo-control, crossover	2	35 (TBI with diffuse axonal injury)	Post-comatose (GCS ≤ 10, mean DRS between 15 and 22)	4 days to 6 weeks	200 mg/day or placebo for 6 weeks then the alternative for 6 weeks	More rapid rate of recovery during amantadine treatment. ↑ MMSE, GOS and ↓ DRS, FIM scores	+
Saniova *et al.* (2004) [52]	Retrospective case-control study	4	41 (TBI)	Persistence unconsciousness (GCS < 8)	< 3 months	200 mg twice daily for 3 days, starting on day 3 of hospitalization in ICU	↑ GCS score, ↓ mortality for amantadine group (n=41) compared to a no treatment group (n=30)	+
Whyte *et al.* (2005) [56]	Longitudinal observational cohort study	4	47 (TBI)	VS/UWS or MCS	< 3 months	Treatment of at least 2 weeks	Greater improvement after treatment than before as assessed with DRS score at 16 weeks post-injury	+

(Table 2) Contd….

Study Author (year) [reference]	Design	Level of evidence	N patients (etiology)	Diagnosis	Time since injury	Treatment procedure	Results	Effect
Hughes *et al.* (2005) [63]	Retrospective cohort study	4	28 (TBI)	« Coma » (*i.e.,* GCS ≤ 5, RLA I-III, no command following)	± 6 weeks	2x100 mg for 1 week, 200 mg 2x/day for 2 weeks	No improvement as compared to a no treatment group (n=95) as assessed by the emergence of coma (*e.g.,* command following), length of coma, length of stay and FIM scores	None
Patrick *et al.* (2006) [59]	Prospective, randomized, double-blind	2	6 (TBI) + 4 who received pramipexol**	"Low-response state" (RLA II-III)	1 to 8 months	50 mg/day for 1 week, 50 mg twice/day for 2 weeks, 50 mg thrice/day for 1 week, 100 mg twice/day for 1 week, 50 mg thrice/day for 1 week, 50 mg twice/day for 1 week	↑ WNSSP, ↓ DRS and CNC scores with ↑ rate of change as compared to pre and post medication baseline	+
Schnakers *et al.* (2008) [67]	Prospective ABAB case study	4	1 (anoxia)	MCS	2 years	3-week baseline, 6-week treatment, 6-week washout, 6-week treatment 200 mg/day	↑ CRS-R scores and ↑ motor activity during first 6-week treatment, ↑ in the frequency of the patient's best CRS-R score during the second 6-week treatment. FDG-PET: ↑ metabolism in dorsolateral prefrontal, temporo-parietal, mesiofrontal cortices, and sensori-motor areas	+
McMahon *et al.* (2009) [60]	Randomized, double-blind, placebo-control, crossover	2	7 (4 TBI, 1 anoxia, 2 stroke) **	VS/UWS or MCS	2 weeks to 3 months	3 weeks of placebo or amantadine, 1 week washout period, 3 weeks of the alternative. 4 mg/kg/day for 1 week followed by 6 mg/kg/day for 2 weeks (max 350 mg/day)	Improvement in arousal and consciousness with subjective evaluations by physician, no objective improvement with CNC and CRS-R	+ and -
Giacino *et al.* (2012) [64]	Prospective multicentric, randomized, double-blind, placebo-control	2	184 (TBI)	VS/UWS or MCS	1 to 3 months	Amantadine or placebo group. 100 mg twice daily for 2 weeks, 150 mg twice daily for 2 weeks (200 mg twice daily for the last week if no improvement), 2 weeks washout	Amantadine group: faster rate of recovery, ↓ DRS scores, ↑ behavioral benchmarks on the CRS-R, and fewer remained in VS/UWS after treatment period	+
Reynolds *et al.* (2013) [65]	Retrospective case series	4	6 (anoxia) + 8 who received methylphenidate, and 2 both	"Persistently comatose"	4 to 35 days	100 mg once or twice daily in ICU	Compared to larger control group (n=112), ↑ survival to hospital discharge, ↑cerebral performance category and modified Rankin scale scores. Compared to nested group (*i.e.*, matched FOUR at 72 hours post injury is ±1, n=16), no difference	None and +
Apomorphine								
Fridman *et al.* (2009) [86]	Case study	4	1 (TBI)	MCS	104 days	± 5 mg ml^{-1}, begins with ratio of 2 mg/$hour^{-1}$ for 12 hours/day up to 8 mg/$hour^{-1}$ for 12 to 16 hours/day for 6 months	Response to command, "yes-no" communication, ↓ CNC, DRS, ↑ GOS scores	+
Fridman *et al.* (2010) [87]	Prospective case series	4	8 (TBI)	VS/UWS or MCS	1 to 4 months	± 5 mg ml^{-1}, begins with ratio of 2 mg/$hour^{-1}$ for 12 hours/day up to 6 mg/$hour^{-1}$ for 12 to 16 hours/day for 6 months	Functional recovery with ↓ CNC and DRS scores, response to command, functional communication for all except 1 patient	+

*N includes the number of patients who received amantadine or apomorphine. **Children. Abbreviations: ↑: improvement/increase; ↓: decrease; TBI: traumatic brain injury; NTBI: non traumatic brain injury, VS/UWS: vegetative state/unresponsive wakefulness syndrome; MCS: minimally conscious state; ICU: intensive care unit; EEG: electroencephalography; FDG-PET: fluorodeoxyglucose positron emission tomography; CNC: Coma/Near-Coma Scale; CRS-R: Coma Recovery Scale-Revised; DRS: Disability Rating Scale; FOUR: Full Outline of Unresponsiveness; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale; MMSE: Mini-Mental Examination Scale; FIM: Functional Independence Measure; RLA: Levels of Cognitive Functioning - Rancho Los Amigos; WNSSP: Western Neuro Sensory Stimulation Profile; WNSE: Western Neurosensory Screening Examination scale; mg: milligram; ml: milliliter. Levels of evidence are considered from [23].

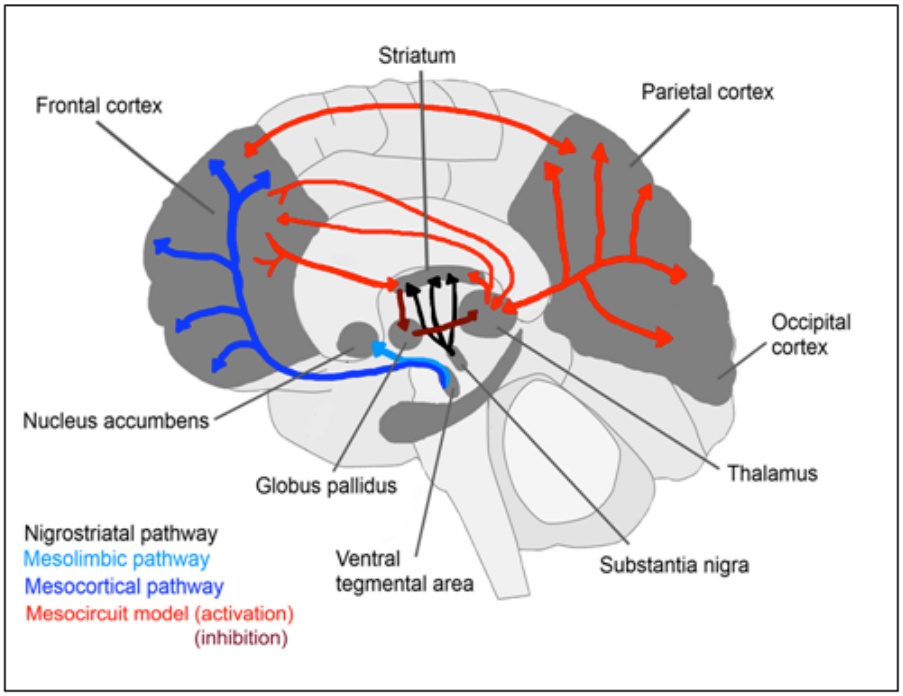

Fig. (2). Schematic illustration of the potential mechanisms of action of dopaminergic agents including amantadine and apomorphine. According to the mesocircuit model [92], dopamine facilitation of the output of the striatum or direct modulation of the frontal cortex would explain the restoration of anterior forebrain activity within the loop connections of the frontal cortex, striatum, pallidum and thalamus. Zolpidem would act more on the globus pallidus by directly inhibiting it (note that in reality it is situated more laterally and higher in the brain).

ing to the recently proposed mesocircuit model by Schiff [92], dopaminergic agents act specifically on the striatum and frontal cortices which will counteract the vulnerability of the anterior forebrain (frontal/prefrontal cortical–striatopallidal–thalamocortical loop systems) following severe brain injury that produces widespread deafferentation or neuronal cell loss. Without projections of the striatum on the globus pallidus by a lack of dopaminergic innervations, the globus pallidus itself will inhibit the central thalamic nuclei, which in turn will inhibit the cortical structures, and this sequence will lead to DOC. The dopaminergic drugs would therefore facilitate projections of the striatum on the globus pallidus which would modulate the frontal cortical neurons, and restore the loops between the frontal cortex, striatum, and central thalamic nuclei [92]. Thalamic modulation effect seems a possible explanation for the fast awakening after amantadine and apomorphine, and is in line with spontaneous recovery from VS/UWS related to the restoration of this thalamo-cortical connectivity [19].

A number of studies also suggest that drugs increasing the brain levels of dopamine or facilitating the action of dopamine can enhance working memory capabilities [93]. Dopamine may be essential for helping to maintain ongoing information despite interference, by signaling when information in working memory should be updated [94]. In more computational terms, one could hypothesize that patients with DOC have more background noise of interference than healthy subjects, and that dopamine could help amplify the signal-to-noise ratio (or facilitate the access to relevant information such as verbal command requests) as well as attenuate the background noise (*e.g.,* irrelevant information such as the surrounding noise). At the same time, the dopamine system has a strong connection to the prefrontal cortex (Fig. **2**), which is critically important for protecting maintained information from distraction. Thus dopamine input to the prefrontal cortex might play a central role in providing that region with interference-protection capabilities that would in turn help patients with DOC to better interact with their surroundings. Finally, dopamine levels seem highly variable across subjects, and hence the neural source of the difference observed among patients with DOC (*i.e.,* some react positively, some do not) might be associated with this variability in the dopamine system (these effects are perhaps genetically based).

ZOLPIDEM

Zolpidem is a non-benzodiazepine short-acting (*i.e.*, half-life of 2.4 hours) hypnotic agent belonging to the imidazopyridine class. It is commonly prescribed as a sleep inducer [95] and is chemically distinct from sedatives such as barbiturates, antihistamines, benzodiazepines and cyclopyrrolones. Zolpidem can also be used as a myorelaxant in neurological pathologies (*e.g.*, catatonia, ataxia, apathy, aphasia, autism, spasticity, Parkinson's [96] and Alzheimer's [97] diseases) and is usually administered orally (or via the feeding tube for non-collaborative patients). This drug has selectivity for stimulating the effect of gamma aminobutyric acid (GABA), and involves various receptors and receptor subtypes. It is the $GABA_A$ receptor chloride channel macro-molecular complex that is implicated in the sedative, anticonvulsant, anxiolytic and myorelaxant properties of zolpidem [98]. While benzodiazepines bind non-selectively to the alpha sub-unit, referred to as the benzodiazepine omega receptors (omega-1, 2, 3), zolpidem has a selective preference for the omega-1 receptors [99, 100]. This binding particularity could explain the paradoxical "awakening" that has been observed for the first time, 13 years ago, in a comatose patient in South Africa [99].

Discovery and Replication of Zolpidem Paradoxical Effects

In 2000, Clauss *et al.* reported an interesting case of the paradoxical positive effects of zolpidem in a "semi-comatose" chronic traumatic patient [99]. After a 10 mg administration in order to reduce the patient's agitation, they were pretty astonished to observe the patient "waking up" by greeting his mother, and providing adequate answers to a series of questions about himself and his environment for the first time since his accident three years before.

The researchers also provided neuroimaging support to these behavioral and cognitive improvements showing that the EEG activity would become responsive to eye opening and the brain single-photon emission computed tomography (SPECT) showed substantial increase of activity in the thalamus, the lentiform and the caudate nuclei. The patient's peak of responsiveness was observed about an hour after the administration of the drug and lasted for a maximum of four hours.

Two years after the publication of this surprising case, the authors wrote a short communication about the patient's overall condition [101]. With a continuous treatment of 10 mg/day, the patient made remarkable cognitive improvements in communication and memory, and his arousal periods had doubled with six to eight hours of awake periods compared to his two to four hours before the start of the treatment. In light of this increase in cognitive functioning with time, the South African team later published a longitudinal zolpidem trial following three chronic patients in VS/UWS for three to six years to further evaluate the drug's efficacy over time. They reported that the drug did not decrease in its efficacy and patients even showed progressive positive improvements since the first day of treatment when assessed with the Glasgow Coma Scale and the RLA cognitive scale. These positive changes were considered significant because the patients (who were previously considered as unconscious) could then respond to simple commands, communicate with their surroundings, eat independently, watch television, and show appropriate emotional responses. Moreover, no deleterious side effects could be observed in the patients after three to six years of daily 10 mg doses. Like reported in the first case study, the peak in responses was observed one hour after the administration, and the patients returned repeatedly to VS/UWS after a maximum of four hours [102].

Clauss *et al.* were the first to publish on the awakening effects of zolpidem in VS/UWS patients, but one could doubt on the accuracy of the diagnosis since the method used for attributing it were not mentioned in their study. They were nevertheless the first to observe that these positive changes could be maintained and increased over time with renewed administration of the drug. In light of these positive outcomes in chronic VS/UWS, Snyman *et al.* performed the first pediatric prospective, double-blind, placebo-controlled randomized trial in three VS/UWS children without successful positive results [103]. The clinical trial consisted of two periods of four days treatment separated by 10 days washout periods, where the children received daily doses of zolpidem or placebo of 0.14 to 0.20 mg/kg. Clinical outcomes were studied with the RLA and the CNC scales as well as with the use of FDG-PET. They reported that the RLA scores showed no change after the administration of the drug while there was an increase in the CNC scores, suggesting a sedative effect consistent with the normal effect of the drug. The study of spontaneous brain metabolic activity showed no changes after zolpidem treatment [103].

Zolpidem in Minimally Conscious Patients

After the publication of the first "miraculous" awakenings in VS/UWS patients, a Scottish team proposed that zolpidem administration should also be explored in other cases of severe brain-injured patients [104]. Thus, they conducted a one-week on/one-week off pharmacological trial in a chronic traumatic MCS patient. An hour after the administration of the drug, the patient was assessed using a wide battery of neuropsychological scales including the Wessex Head Injury Matrix, the RLA and the Western Aphasia Battery (WAB) and no positive neurological changes could be objectified [104]. In the absence of cognitive improvements in the first clinical trial with a MCS patient, the authors suggested that the underlying mechanisms of zolpidem could be mediated differently in patients showing less neuronal damage and expressing a higher functional level. The authors' conclusion was later challenged by the observation of subsequent behavioral improvements in a chronic anoxic MCS patient in Israel [105]. At baseline, the patient described in Shames *et al.*'s was able of sustained eye contact, simple verbalizations and accurate responses to simple commands such as "move your legs". In order to improve the motor and cognitive status as well as the lack of cooperation, the patient was first given a 10 mg dose of zolpidem. Positive effects could be observed after 30 minutes and could last for about 3 hours. The patient showed an increased score when assessed with the RLA, was able of speaking short sentences, showed appropriate emotional responses, and was entirely collaborating. Improvements in communication skills also permitted to objectify memory impairments although she could remember basic information about herself and her family's history. The positive effects were also observed under a lower dosage (5 mg) but remained inconsistent [105]. Shames *et al.*'s study was the first to identify a zolpidem responder in a MCS patient. In line with these results, Cohen *et al.* later published the case of another chronic anoxic patient in MCS who was not responding to previous methylphenidate, levodopa/carbidopa and antidepressants trials, and who was more responsive after a zolpidem morning dose of 5 mg. The dose was then increased to a 10 mg intake in the morning and a 5 mg intake in the afternoon during a continuous three-week period. Following this treatment plan, the patient became able of structured speech, social interactions with family and medical staff. He could also eat independently and was able to collaborate in various activities. Furthermore, the zolpidem treatment permitted him to be discharged and to go home. Again, the beneficial effects were only present under the drug's action and the patient could not sustain a higher functional level on his own without treatment. However, the therapeutic effects were more robust three months after discharge following a treatment plan of 20 mg a day (*i.e.*, divided into intakes of 10 mg in the morning and 10 mg in the afternoon) [106].

Etiology and Zolpidem Treatment

Previously reported clinical trials showed that zolpidem responders can be found in patients with DOC from both anoxic and traumatic etiologies (Table **3**). In order to further assess the efficacy of zolpidem treatment according to the patients' site of injury, a Chinese team recently studied 127 subacute patients in VS/UWS over a one-week daily treatment. They divided the patients into four groups based on the mechanisms of their injuries, mainly in two non-brainstem injury (*i.e.*, brain countercoup contusion and brain compression injury) and two brainstem injury groups (*i.e.*, primary and secondary brainstem injuries). The observations also included SPECT measures and digital cerebral state monitoring (*i.e.,* a non-invasive electronic tool to measure the patients' level of consciousness based on spontaneous EEG recordings with burst suppression and electromyogram indices). Under zolpidem, the level of consciousness (assessed with the digital monitoring recordings and the burst suppression scores) of the non-brainstem injury groups were better than those before treatment whereas no significant changes were observed for the brainstem injury groups. The electromyogram recordings before and after zolpidem treatment were not different across the different groups after an hour. SPECT measures showed an increased perfusion in brain-damaged areas in the non-brainstem injuries groups while no changes could be observed in the remaining two groups. From these results, the authors concluded that zolpidem could have positive effects on brain functions in non-brainstem injuries since the latter might be more reversible than brainstem injuries. They also suggested that the positive effects observed on brain perfusion and consciousness quantitative indicators after the administration of the drug were rather sudden than gradual. Indeed, the comparison of the patients parameters after one day of treatment or after one week of treatment did not show any significant difference [107]. This study also clearly illustrates that pharmacological agents can have reduced or optimized effects depending on the brain site and the mechanism of injury.

On-off or Gradual Phenomenon?

In order to determine the rate of responders among the DOC population as well as to identify possible subtler signs of behavioral changes in non-responders, a recent prospective double-blind placebo controlled crossover design study was conducted among 15 subacute and chronic patients with DOC (12 VS/UWS and 3 MCS patients) [108]. These patients from various etiologies were assessed with the CRS-R before and after a 10 mg administration of zolpidem or placebo. After the administration of the drug, only one chronic traumatic patient in VS/UWS demonstrated clear signs of cognitive improvements (6.7% of the recruited sample). He could respond to simple commands, grab objects, show visual fixation and pursuit, and wave at the examiner. These results were considerable since they were compatible with a MCS diagnosis rather than the previous VS/UWS diagnosis. As for the observation of more subtle behavioral changes in the 14 non-responders, none could be observed suggesting that zolpidem would have "all-or-none" or biphasic therapeutic properties rather that some ranging effects on a continuum. Indeed, so far the rare transient awakenings of patients with DOC under zolpidem treatment remained observed to operate as a "switch" mechanism, and that adding up administrations during the day would not produce increasing effects [106]. In parallel, most of the changes observed in the above studies followed an administration of 10 mg zolpidem. However, after a zolpidem trial with demented patients, it has been suggested that lesser doses in adults may achieve a similar result [97], but only one documented DOC case study could demonstrate inconsistent recovery of consciousness with a morning dose of 5 mg [106]. Further studies are therefore needed to replicate this observation and to determine the lower-dose responders' clinical features. Counter to the "on-off" proposed mechanism, an EEG study conducted by Machado *et al.* in a post-stroke chronic VS/UWS patient showed that zolpidem could produce less dramatic changes [109]. In fact, after 20 minutes post-administration, the patient could open her eyes sustainably and she started yawning a few minutes later. Interestingly, the investigators found that the yawns were correlated with subdelta bands, which were more ample before the observed behavior. They also observed an increase in delta power after the yawning period and a decrease before that aroused period (see next chapter for more details). Thus, this case report suggests that although improvements following a zolpidem intake take place rather suddenly (*i.e.*, after more or less 30 minutes), it might lead in some cases to more subtle improvements in the patient's condition. It also highlights the importance of using parallel neurophysiological measures in the evaluation of the patient conditions for objectifying subtler changes. With the aim of better characterizing behavioral changes as well as estimating the frequency of positive effects post-administration of zolpidem, our team recently conducted a clinical trial in 60 traumatic and non-traumatic chronic patients with DOC (31 with TBI; 32 in MCS, 28 in VS/UWS) [110]. According to repetitive assessments with the CRS-R, only one traumatic patient in MCS (1.6% of our sample) showed behavioral improvements (*i.e.,* functional use of objects which is consistent with the diagnosis of emergence from MCS). Following this performance, the patient was then re-observed for a double-blind placebo controlled trial but then failed to show any clinical improvement. Interestingly, among the non-responders, 12 patients (20%) were found to have increased total scores at the post-zolpidem behavioral assessment, suggesting that the drug could have induced subtler changes in them. However, since the presence of spontaneous arousal fluctuations in patients with DOC could also be attributable to these changes, the post-zolpidem scores were also compared with the best score obtained during the repetitive CRS-R assessments without zolpidem. From that comparison, we observed that four patients (6.7%) functionally improved (*i.e.*, demonstrating automatic motor reaction, command following, vocalizations) although without being important enough to change their diagnosis (according to the CRS-R guidelines). The observations from this study thus fall within the hypothesis that zolpidem could lead to more subtle and possibly gradual effects in some patients. These effects should be more closely recorded in future prospective and longitudinal studies and these positive behavioral changes could be labeled as *small* (*i.e.*, increase in arousal), *medium* (*i.e.*, responsiveness improvement but same diagnosis) or *significant* (*i.e.*, change of diagnosis).

Motivational Processes

Several studies were interested in the mechanisms involved in the waking effects of zolpidem in brain-damaged patients (Table **3**). SPECT studies showed that zolpidem could increase the cerebral metabolism in hypoactive areas following traumatic or anoxic lesions [99, 102, 107]. Similarly, FDG-PET data in three chronic post-anoxic MCS patients showed metabolic level increases in a set of hypoactive areas encompassing the limbic loops (*i.e.*, orbitofrontal cortex), possibly modulating motivational processes. Behaviorally, all three patients recovered a functional communication after administration of zolpidem as assessed with the CRS-R [111]. In parallel to these findings, zolpidem has also been observed to induce improvements in patients with akinetic mutism. By definition, akinetic mutism patients are left with a lack of initiation of goal-directed behaviors and communication, and can sometimes be mistakenly diagnosed as being unconscious [112, 113]. These patients usually have lesions in mesiofrontal regions and represent a subgroup of MCS patients [114]. In 2007, a French team published their work on motor and neuropsychological improvements in a patient with chronic hypoxic encephalopathy akinetic mutism [115]. Using FDG-PET scan, they observed an increase in cerebral metabolism in the patient's postrolandic territories and in frontal cortex after a 20 mg administration of zolpidem during a resting state condition. In parallel, brain metabolism measurements using $H_2{}^{15}O$ PET technique were also gathered during an active object-naming task, and showed drug-induced activations mainly localized in the anterior cingulate and orbitofrontal cortices while the patient was able to correctly name objects. Behaviorally, after the administration of zolpidem, the patient was able to eat, communicate with her family, stand up and walk. Finally, she also showed post-treatment neuropsychological improvements in language assessments. All the described improvements in the patients' behavioral and cognitive functions were under the drug's action while the placebo trial did not induce any positive changes in her performance. The positive effects started after 20 minutes and lasted for two to three hours. However, contradictory results have been further published by a Chinese team who followed two subacute (*i.e.*, four weeks post-insult) hypoxic encephalopathy patients in VS/UWS with similar hypoxic brain lesions but without the diagnosis of akinetic mutism. Following a 10 mg administration of zolpidem on two different assessment trials, the patients failed to show any functional improvement [116]. The authors stipulated that the absence of positive findings could be the result of possible discrepancies of their patients' functional baseline status (*i.e.*, the duration of hypoxia and the brain's structural damage).

Zolpidem has been proposed to interact with the brain's limbic loops by modulating subcortical connections, and more particularly at the level of the globus pallidus. Because of its action on the thalamus and on cortical regions (particularly at the prefrontal level), this region has been previously identified as functionally linked to arousal and awareness levels. According to Schiff's mesocircuit model (see Fig. **2**, [117]), zolpidem could have a direct influence on the limbic system loops by modulating cortical and subcortical connections especially at the striatum and globus pallidus levels. In fact, previous studies have identified large populations of $GABA_A$ alpha-1 subunit in these subcortical brain regions [118]. When they are activated, they would bring the thalamocortical activity back to normal and would allow the recovery of consciousness. Thus, when neuronal activity in the striatum is reduced as a consequence of brain injury, central thalamic activity is also reduced. Interestingly, it seems that the neurons from these regions

are far more vulnerable to hypoxic injuries [56], and in support of this experimental observations, many of the reported zolpidem responders case studies include patients with hypoxic-anoxic brain injuries [105, 106, 111, 115, 116].

The Neuronal Dormancy and the Neuronal Desynchronization Mechanisms

The spectacular effects of zolpidem have also been attributable to the awakening of "sleeping" brain regions. In fact, a mechanism of neuronal dormancy was introduced to explain the effects of zolpidem: certain nonspecific areas of the brain, adjacent or distant to the initially damaged zones (*e.g.*, the ipsilateral, contralateral hemisphere, or the cerebellum), can be inhibited after the brain insult. During the acute phase, the neuroprotective dormancy mechanism gives rise in GABA levels in order to reduce and suppress brain activity and excitotoxicity in order to facilitate the recovery of brain tissue or to prevent from more neuronal loss [119, 120]. Transient recovery of consciousness would be mediated by a selective omega-1 GABA-agonistic action in the reversal of that neuronal dormancy observed following brain injury. When the patient enters the chronic phase, GABA levels will go back to normal or show a slight decrease, but the neuroprotective GABA mechanism can still be present and prevent the functional activity of critical brain regions for the emergence of consciousness [121]. The inconsistency and the rarity of the effects could therefore be explained by the high specific action of the substance on viable dormant brain regions and thus, in cases of more extensive brain injuries (*i.e.*, that are not due to a protective decrease in brain functional activity but rather to the permanent destruction of the critical regions for arousal and awareness), zolpidem as well as other pharmacological treatments would not produce therapeutic effects [102].

A second way in which zolpidem contributes to the restoration of arousal and cognitive functions would be attributable to its neuronal desynchronization restoration property. After severe damage to the brain, the neural activity loses its power of complex information integration (resulting from desynchronization among neuronal population) and enters a state of homogeneous synchronization [122]. This increasing pathological synchronization is observed with the presence of slow wave activity across the cortex, and is associated with cognitive declines and neuropathological altered states of consciousness [123]. A recent single case behavioral and neuroimaging investigation on a conscious patient with chronic stroke illustrates that mechanism. When given a single 5 mg dose of zolpidem, the patient showed clear behavioral and cognitive improvements and these changes were correlated with the suppression of pathological slow waves (theta and beta frequency) as observed with magnetoencephalography. Moreover, as reported in previous studies, SPECT showed an increase in cerebral blood perfusion in the main lesional site (*i.e.,* left temporal lobe lesion including language and motor areas) after treatment with zolpidem [124].

CONCLUSIONS

Pharmacological treatments of patients with DOC currently aim to improve arousal levels and recovery of consciousness. The purpose of this paper was to provide a systematic overview of the therapeutic effects and underlying mechanisms of commonly prescribed pharmacological agents in patients with DOC: amantadine, apomorphine and zolpidem. Even if the underlying mechanisms of action of these drugs remain unclear, preliminary evidence from clinical trials suggests positive changes in the patients' neurological status leading sometimes to dramatic improvements [64, 87, 99, 108].

Amantadine and apomorphine are dopaminergic agonists, which, each in its own way, provide some positive effects in patients with DOC. On the one hand, the action of amantadine (which is an NMDA antagonist and an indirect dopamine agonist) can be observed within a few days to weeks after administration. Its effects on functional recovery have been reported within 4 weeks after treatment initiation and have been observed to last up to 2 weeks post-treatment [64]. Positive effects have been reported both in VS/UWS and MCS patients especially in chronic TBI cases although some therapeutic effects have also been observed in patients with anoxia. Amantadine has been hypothesized to enhance the transmission in nigrostriatal, mesolimbic, mesocortical and/or thalamic circuits and is associated with increased alpha activity together with decreased theta activity, and increased metabolic activity in the fronto-parietal network [66, 67]. On the other hand, apomorphine acts directly as a non-selective dopaminergic agonist and its effects are observed more rapidly than those of amantadine. Compared to amantadine, apomorphine has been studied less extensively in patients with DOC. The two studies using it report a favorable outcome (reproducible responses to command and functional communication) in a MCS patient; when administered to both patients in MCS and VS/UWS all but one patient showed functional communication [86, 87]. These patients were of traumatic etiology, which might be the most suitable target for apomorphine. However, given the small number of patients studied under uncontrolled experimental settings, the mechanisms of apomorphine remain unclear.

Zolpidem, a non-benzodiazepine short-acting hypnotic agent belonging to the imidazopyridine class has been reported to act within an hour after its administration and has effects that last up to four hours. Despite the miraculous recoveries initially reported in patients in VS/UWS, the reported outcome was less favorable when tested under more controlled settings. In some MCS patients, zolpidem administration led to important functional recoveries such as responses to command, speech recovery, emotional responses and functional communication [105, 115]. The reported responders' case studies included patients with anoxic-hypoxic and traumatic brain injuries. Zolpidem intake has been shown to enhance metabolic activity as well as perfusion in damaged brain areas [107, 115], and it may interact with the brain's limbic loops by modulating cortical and subcortical connections (globus pallidus playing a key role) [92].

Based on the Common Terminology Criteria for Adverse Events [22], the reported side effects of the drugs in question were considered as mild (grade 1), moderate (grade 2), or on a few occasions as severe (grade 3) but they were never classified as life threatening. In most cases, the exposure to amantadine or apomorphine did not increase the risk of adverse events, and besides drowsiness, zolpidem did not induce any other deleterious side effect. Based on the Oxford Levels of Evidence, which relies on the source type (*e.g.,* randomized trial, case-series) [23], five studies with amantadine and apomorphine and two with zolpidem were considered as level II, but only the study by Giacino *et al*. included a large cohort of TBI patients showing a faster rate of recovery with amantadine compared to placebo [64]. For zolpidem, only one of the two small cohorts' randomized studies reported a positive outcome [108]. In our view, evidence quality should also take into account the number of patients included in a study, the type of assessment tool, and the clinical relevance to fully appreciate the results obtained across the different studies.

To date, no definite pharmacological therapy can be planned for a particular therapeutic option for patients with DOC because of insufficient evidence. First, most studies include small cohorts. Second, the existing clinical trials do not always use optimal standardized evaluation of consciousness. Standardized assessments with sensitive tools capture the more subtle changes in the recovery of awareness after drug administration. These changes may only be observed at the arousal level but are worth investigation since in some cases, aroused patients can demonstrate signs of higher-level brain functioning. Third, the fact that existing clinical trials do not use a common metric of consciousness recovery does not allow for

Table 3. Studies on zolpidem treatment in patients with disorders of consciousness.

Study (year) [reference]	Design	Levels of evidence	N patients (etiology)	Diagnosis	Time since injury	Treatment procedure	Results	Effect
Clauss *et al.* (2000) [99]	Case study	4	1 (TBI)	Semi-comatose	3 years	10 mg for 2 days, repeated once 2 days later	Verbal response after 15 minutes, talking, answering simple questions, spontaneous interaction, counting, writing. SPECT: ↑ blood perfusion in the thalamus, the lentiform and the caudate nuclei	+
Clauss *et al.* (2001) [101]	Case study from 2000	4	1 (TBI)	Semi-comatose	5 years	10 mg daily for 2 years	Long-term positive effects. ↑ arousal, awake periods, memory and communication skills	+
Clauss & Nel (2006) [102]	Case series	4	3 (2 TBI, 1 anoxia)	VS/UWS	3 to 5 years	10 mg daily for 3, 5 et 6 years	↑ arousal, GCS and RLA scores. SPECT (1 patient with TBI): ↑ blood perfusion in frontal regions bilaterally, reversal of the left sided cerebellar diaschisis	+
Brefel-Courbon *et al.* (2007) [115]	Random, double-blind, placebo-control case study	4	1 (anoxia)	MCS	2 years	20 mg daily for 1 week	↑ arousal, motor and neuropsychological performance (functional communication, eating, walking, reading and repeating words). FDG-PET: ↑ in postrolandic territories and frontal cortex. $H_2{}^{15}O$-PET: ↑ anterior cingulate and orbitofrontal cortices	+
Lo *et al.* (2008) [116]	Case series	4	2 (hypoxia)	VS/UWS	± 1 month	10 mg for 2 days, repeated once 2 days later	No arousal improvement, no recovery of consciousness, no ↑ GCS score	None
Singh *et al.* (2008) [104]	Case study	4	1 (TBI)	MCS	4 years	10 mg daily for 1 week	No overall ↑ in performance at different neuropsychological tests and ↓ in performance for two of the tests	None and -
Shames & Ring. (2008) [105]	Case study	4	1 (anoxia)	MCS	18 months	10 mg repeated for several days in a row. Trials with 5 mg	↑ lucidity, RLA score, reading, counting, autoalimentation, verbal production and communication	+
Cohen & Duong (2008) [125]	Case study	4	1 (anoxia)	MCS	8 months	5 mg then 10 mg daily for 3 weeks then 20 mg daily	↑ lucidity, interactions, verbal and social responses	+
Whyte *et al.* (2009) [108]	Multicentric, randomized, double-blind, placebo-control	2	15 (8 TBI)	VS/UWS or MCS	3 months to 23 years	10 mg once (and once placebo)	Only 1 patient with TBI responded to treatment (VS/UWS to MCS), ↑ score CRS-R, visual pursuit, response to command	None and +
Snyman *et al.* (2010) [103]	Double-blind, randomized placebo-control	2	3 (1 TBI)*	VS/UWS	2 years to 13 years	0.14 – 0.2 mg/kg for 2 treatments of 4 days, separated by 10 days	↓ responsiveness, no difference with placebo	None and -
Machado *et al.* (2011) [109]	Case study	4	1(stroke)	VS/UWS	5 years	10 mg single dose	↑ arousal (sustained eyes opening, yawning) associated with EEG and electrocardiogram changes but no recovery of consciousness	±
Du *et al.* (2013) [107]	Prospective open-label cohort study	3	127 (32 TBI)	VS/UWS	± 1 month	10 mg daily for 1 week	↑ cerebral state index in brain contrecoup and space-occupying brain compression injuries groups as measured by a digital cerebral state monitor. SPECT: ↑ blood perfusion in damaged areas in the non-brainstem injuries groups	+

(Table 3) Contd….

Study (year) [reference]	Design	Levels of evidence	N patients (etiology)	Diagnosis	Time since injury	Treatment procedure	Results	Effect
Thonnard *et al.* (2013) [110]	Prospective open-label cohort (including double-blind placebo-control for 1 patient)	3	60 (31 TBI)	VS/UWS or MCS	4 ± 5.5 years	10 mg single dose	Change of diagnosis in 1 patient (functional use of object - not reproducible), ↑ CRS-R scores in 4 patients without change of diagnosis (*e.g.,* automatic motor reaction, vocalizations)	None and +

Abbreviations: VS/UWS: vegetative state/unresponsive wakefulness syndrome; MCS: minimally conscious; TBI: traumatic brain injury; mg: milligram; kg: kilograms; ↑: improvement/increase; ±: more or less; ↓: decrease; RLA: Ranchos Los Amigos Scale; CRS-R: Coma Recovery Scale-Revised; FDG-PET: fluorodeoxyglucose positron emission tomography; SPECT: single-photon emission computed tomography. *Children. Levels of evidence are considered from [23].

multi-center comparisons of the treatment's efficacy. In future studies, we suggest including all clinical entities across the spectrum of consciousness in a study's baseline diagnosis (coma, VS/UWS, MCS+, MCS-) so as the behavioral responses to the pharmacological agents accurately reflect the treatment effect and not a baseline's misdiagnosis. We also recommend combining the use of sensitive and specific behavioral tools (*e.g.*, CRS-R) with neuroimaging and electrophysiology measurements in randomized, double-blind, placebo-controlled experimental designs. At the clinical level, since there are only a few therapeutic options available and few reported side effects, different pharmacological treatments should be tested in a patient with DOC (note to use caution with patients who have a history of seizure for amantadine treatment).

To conclude, therapeutic pharmacological treatment in patients with DOC is in its infancy. Amantadine, apomorphine and zolpidem have nevertheless show beneficial effects in some adults and pediatric populations with DOC. More research is needed to determine which treatment would provide the best neurological outcome regarding the patient's etiology, diagnosis, time since injury and overall condition. Large multi-center studies, using common behavioral metrics combined with state-of-the-art neuroimaging and/or electrophysiology techniques, are expected to shed more light on the underlying mechanisms of these drug treatments and eventually determine an evidence-based model for the pharmacokinetics and pharmacodynamics of these agents in severely brain injured, non-communicative patients.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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ABBREVIATIONS

CRS-R = Coma Recovery Scale-Revised
DOC = Disorders of consciousness
DRS = Disability Rating Scale
EEG = Electroencephalography
FDG-PET = Fluorodeoxyglucose positron emission tomography
FOUR = Full Outline of Unresponsiveness Scale
GCS = Glasgow Coma Scale
GABA = Gamma-Aminobutyric acid
ICU = Intensive care units
MCS = Minimally conscious state
PET = Positron emission tomography
RLA = Ranchos Los Amigos scale
SPECT = Single-photon emission computed tomography
TBI = Traumatic brain injury
VS/UWS = Vegetative state/unresponsive wakefulness syndrome
WHIM = Wessex Head Injury Matrix
WNSSP = Western Neuro Sensory Stimulation Profile

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