

# Best Practice Guidelines for the Use of Pharmacological Neuromodulation in Disorders of Consciousness: A Comprehensive Approach

## Abstract

Disorders of consciousness (DOC) are severe acquired brain injuries leading to arousal, awareness, and responsiveness alterations. Traditionally, DOC comprised three distinct states: coma (or comatose state), vegetative state/unresponsive wakefulness syndrome (VS/UWS), and the minimally conscious state [1]. The MCS can be further divided into MCS “plus” (MCS1) or MCS “minus” (MCS) based on the presence or absence of language abilities. A movement within the field proposes to include the PTCS as the fourth state of DOC. [1]

Dopaminergic agonists are among the most studied medicines in DOC. Dopaminergic medicines studied as treatments for DOC include amantadine, bromocriptine, apomorphine, and levodopa (commonly combined with carbidopa). Amantadine initially came to market in the 1960s as an antiviral agent used to treat and prevent influenza type A. Its dopaminergic properties later led to its use as an antiparkinsonian agent. There is now a high level of evidence to use Amantadine to facilitate recovery in disorders of diminished consciousness and some preliminary evidence with Baclofen and Zolpidem [1].

Other pharmacological agents used include Methylphenidate, pramipexole, Bromocriptine, Modafinil, etc, with some evidence. The literature widely discusses the use of different pharmacological medications with dopaminergic potentiation, but what was lacking was a standardized protocol for using medications depending on the stages of recovery.

The author reviewed various published materials and concluded that clinical practice guidelines for using these dopaminergic agents to facilitate recovery in disorders of diminished consciousness were generally lacking and required clarity regarding when and how to use these medications depending on stages of brain injury recovery.

The article proposes practical best practice guidelines following a review of existing literature, adopts the Ranchos amigos recovery scale, and

## Review Article

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correlates the recovery process with appropriate dopaminergic pharmacological intervention to facilitate recovery. The author also proposes naming this “Brain Injury Recovery Guidelines” to get some traction and visibility in using structured guidelines with DOC.

## Objectives

The principal objective is to establish best practice guidelines for using dopaminergic agents to facilitate recovery in disorders of consciousness, using the Ranchos Los Amigos scale as an outcome measure.

Secondly, to assess the currently available literature and study the usefulness of dopaminergic medications, outline safety parameters and risk profile, and come up with structured, standardized, simple, user-friendly guidelines based on available evidence with dopaminergic agents and their therapeutic use in adults with acquired brain injury and review the functional outcomes, cognitive function, and reduce mortality.

## Methodology

The methodology is to review the existing literature and determine if there are any established guidelines for using dopaminergic agents against neurological recovery using a standardized scale. The Rancho Los Amigos Scale (RLAS) is a widely used tool to assess the cognitive and behavioural recovery of patients with brain injuries. It ranges from Level I (No Response) to Level X (Purposeful-Appropriate). The author proposes a treatment protocol using dopaminergic agents tailored to various Rancho Los Amigos Scale levels.

## Evidence and guidelines

- **Clinical evidence:** Review clinical studies and guidelines supporting the use of specific dopaminergic agents in TBI recovery. Agents like amantadine have substantial evidence supporting their use in improving cognitive and motor functions [2].
- **Guidelines:** To inform your choice, refer to clinical practice guidelines from reputable organizations, such as the Brain Trauma Foundation or Cochrane Reviews [3].

## Treatment protocol using dopaminergic agents based on rancho los amigos scale

### Level I: No Response.

- **Description:** Patient shows no response to stimuli.
- **Treatment focus:** Stabilization and prevention of complications.
- **Dopaminergic agents:** Not typically initiated at this stage. Focus on supportive care.

### Level II: Generalized Response.

- **Description:** Patient reacts inconsistently and non-purposefully to stimuli.
- **Treatment focus:** Begin minimal stimulation and monitor for any signs of increased responsiveness.
- **Dopaminergic agents:** Consider starting low-dose amantadine to stimulate arousal and responsiveness.
- **Dosage:** Amantadine 100 mg once daily, titrate based on response and tolerance.

### Level III: Localized Response.

- **Description:** Patient responds specifically but

inconsistently to stimuli.

- **Treatment focus:** Enhance arousal and attention.
- **Dopaminergic agents:** Continue or initiate amantadine, consider adding methylphenidate for attention.
- **Dosage:** Amantadine 100 mg twice daily.  
Methylphenidate 5 mg once daily, titrate up to 10 mg twice daily based on response.

### Level IV: Confused-Agitated.

- **Description:** Patient exhibits heightened state of activity with confusion and agitation.
- **Treatment focus:** Manage agitation and improve cognitive function.
- **Dopaminergic agents:** Use amantadine to reduce agitation and improve cognitive function.
- **Dosage:** Amantadine 100 mg twice daily, may increase to 200 mg twice daily if tolerated.

### Level V: Confused-Inappropriate, Non-Agitated.

- **Description:** Patient is confused and responds inaccurately to commands.
- **Treatment Focus:** Improve attention and reduce confusion.
- **Dopaminergic Agents:** Continue amantadine. Consider adding bromocriptine for cognitive enhancement.
- **Dosage:** Amantadine 100-200 mg twice daily.

Bromocriptine 1.25 mg once daily, titrate up to 2.5 mg twice daily.

### Level VI: Confused-Appropriate.

- **Description:** Patient shows goal-directed behaviour but requires external input for direction.
- **Treatment focus:** Enhance cognitive function and independence.
- **Dopaminergic agents:** Continue the current regimen; consider adding levodopa/carbidopa for motor and cognitive benefits.
- **Dosage:** Amantadine 100-200 mg twice daily.

Bromocriptine 2.5 mg twice daily.

Levodopa/Carbidopa 100/25 mg three times daily.

### Level VII: Automatic-Appropriate.

- **Description:** Patient performs daily routines automatically but lacks insight into condition.

- **Treatment focus:** Improve insight and higher cognitive functions.
- **Dopaminergic agents:** Maintain current regimen, consider increasing doses if cognitive plateau occurs.
- **Dosage:** Adjust based on patient response and tolerance.

**Level VIII:** Purposeful-Appropriate (Standby Assistance)

- **Description:** Patient is aware of and responsive to the environment but requires assistance.
- **Treatment focus:** Enhance executive functions and independence.
- **Dopaminergic agents:** Continue the current regimen, monitor for side effects, and adjust as needed.
- **Dosage:** Maintain or adjust based on clinical response.

**Level IX:** Purposeful-Appropriate (Standby Assistance on Request).

- **Description:** Patient can perform tasks independently but may need assistance upon request.
- **Treatment focus:** Fine-tune cognitive and executive functions.
- **Dopaminergic agents:** Continue current regimen, consider tapering if stable.
- **Dosage:** Gradual tapering of dopaminergic agents if cognitive functions are stable.

**Level X:** Purposeful-Appropriate (Modified Independent).

- **Description:** Patient functions independently with compensatory strategies.
- **Treatment focus:** Maintain cognitive function and monitor for long-term side effects.
- **Dopaminergic agents:** Consider discontinuation if patient maintains stable cognitive function without medication.
- **Dosage:** Taper off dopaminergic agents under medical supervision.

## Medications and dosage guidelines

### Amantadine

- **Initial dose:** Start with 100 mg once daily.

- **Titration:** Increase to 100 mg twice daily after 1 week if tolerated.
- **Maximum dose:** Can be increased to 200 mg twice daily if needed and tolerated.
- **Adjustment considerations:** Monitor for side effects such as dizziness, insomnia, and agitation. If side effects occur, consider reducing the dose or discontinuing the medication.

### Methylphenidate

- **Initial dose:** Start with 5 mg once daily.
- **Titration:** Increase by 5 mg increments every week based on response and tolerance.
- **Maximum dose:** Up to 10 mg twice daily.
- **Adjustment considerations:** Monitor for side effects such as increased heart rate, blood pressure, and anxiety. Adjust the dose accordingly or consider an alternative agent if side effects are problematic.

### Bromocriptine

- **Initial dose:** Start with 1.25 mg once daily.
- **Titration:** Increase to 2.5 mg once daily after 1 week if tolerated.
- **Maximum dose:** Increase to 2.5 mg twice daily if needed.
- **Adjustment considerations:** Monitor for side effects such as nausea, orthostatic hypotension, and headaches. Gradually increase the dose to minimize side effects.

### Levodopa/Carbidopa

- **Initial dose:** Start with 100/25 mg three times daily.
- **Titration:** Increase by 100/25 mg weekly based on response and tolerance.
- **Maximum dose:** Up to 200/50 mg thrice daily.
- **Adjustment considerations:** Monitor for side effects such as dyskinesia, nausea, and orthostatic hypotension. Adjust the dose or frequency as needed [4].

### Pramipexole

- **Mechanism:** A dopamine agonist that selectively stimulates dopamine D2 and D3 receptors.
- **Uses:** Commonly used in treating Parkinson's disease and restless legs syndrome.

- **Potential benefits in TBI:** May help improve motor function and cognitive recovery by enhancing dopaminergic transmission.

### Ropinirole

- **Mechanism:** A dopamine agonist that primarily stimulates dopamine D2 receptors.
- **Uses:** Used for Parkinson's disease and restless legs syndrome.
- **Potential benefits in TBI:** Modulating dopamine pathways can improve motor and cognitive functions.

### Rotigotine

- **Mechanism:** A dopamine agonist delivered via a transdermal patch provides continuous dopamine receptor stimulation.
- **Uses:** Used for Parkinson's disease and restless legs syndrome.
- **Potential benefits in TBI:** Continuous delivery may help maintain stable dopaminergic activity, potentially aiding cognitive and motor recovery.

### Apomorphine

- **Mechanism:** A potent dopamine agonist that stimulates dopamine receptors directly.
- **Uses:** Used for advanced Parkinson's disease to manage "off" episodes.
- **Potential benefits in TBI:** It may provide rapid improvement in motor function and alertness, though its use is limited by side effects such as nausea and hypotension.

### Cabergoline

- **Mechanism:** A long-acting dopamine agonist that stimulates dopamine D2 receptors.
- **Uses:** Used for hyperprolactinemia and Parkinson's disease.
- **Potential benefits in TBI:** Long-acting properties may provide sustained dopaminergic stimulation, potentially aiding recovery.

### Lisuride

- **Mechanism:** A dopamine agonist with additional serotonergic and adrenergic activity.
- **Uses:** Used for Parkinson's disease and migraine prophylaxis.
- **Potential benefits in TBI:** It may help improve cognitive and motor functions through its multi-

receptor activity.

### Quinpirole

- **Mechanism:** A selective dopamine D2 and D3 receptor agonist.
- **Uses:** Primarily used in research settings to study dopaminergic function.
- **Potential benefits in TBI:** Experimental use suggests potential benefits in enhancing dopaminergic transmission and cognitive recovery.

### Pergolide

- **Mechanism:** A dopamine agonist that stimulates both D1 and D2 receptors.
- **Uses:** Previously used for Parkinson's disease (withdrawn in some markets due to cardiac valve issues).

### General principles for dosage adjustments

1. **Start low, go slow:** Begin with the lowest effective dose and gradually increase based on patient response and tolerance.
2. **Monitor closely:** Regularly assess the patient's cognitive and functional status and any side effects.
3. **Individualize treatment:** Adjust dosages based on patient needs, considering age, weight, renal function, and comorbidities.
4. **Side effect management:** If side effects occur, consider dose reduction, slower titration, or switching to an alternative dopaminergic agent.
5. **Regular follow-up:** Schedule regular follow-up visits to reassess the patient's progress and adjust the treatment plan as needed.

### Monitoring parameters

- **Cognitive function:** Use neuropsychological tests to assess attention, memory, and executive function improvements.
- **Functional outcomes:** Evaluate using the Disability Rating Scale (DRS) or Glasgow Outcome Scale (GOS).
- **Side effects:** Regularly check for common side effects like nausea, dizziness, insomnia, and agitation.

### Adverse events and side effects

- **Common side effects:** Monitor for nausea, dizziness, insomnia, agitation, orthostatic



hypotension, and headaches. Document any occurrences and adjust dosages accordingly.

- **Serious adverse events:** Be vigilant for more severe reactions such as cardiac arrhythmias, severe hypertension, or neuroleptic malignant syndrome (rare but serious).

### Example monitoring schedule

- **Week 1-2:** Initial assessment and baseline measurements.
- **Week 3-4:** Follow-up visit to assess initial response and side effects. Adjust dosages if necessary.
- **Month 2-3:** Regular follow-up visits to monitor progress, side effects, and adherence.
- **Month 4-6:** Continue regular monitoring, with adjustments based on patient response and tolerance.
- **Long-Term:** Periodic assessments every 3-6 months to ensure sustained benefits and monitor for long-term side effects [4].

When using dopaminergic agents for the management of traumatic brain injury (TBI), it is crucial to monitor for common side effects to ensure patient safety and adjust treatment as necessary. Here are some common side effects associated with these medications:

### Amantadine

- **Nausea and vomiting:** Gastrointestinal discomfort is common, especially at higher doses.
- **Dizziness:** Patients may experience light-headedness or dizziness, particularly when standing up quickly.
- **Insomnia:** Difficulty sleeping or disturbances in sleep patterns.
- **Agitation and anxiety:** Increased restlessness or nervousness.
- **Orthostatic hypotension:** A drop in blood pressure upon standing, leading to dizziness or fainting.
- **Peripheral Edema:** Swelling of the extremities, such as the hands and feet [2].

### Methylphenidate

- **Increased heart rate and blood pressure:** Monitor cardiovascular status regularly.
- **Appetite suppression:** Reduced appetite, which can lead to weight loss.

- **Insomnia:** Difficulty falling or staying asleep.
- **Anxiety and nervousness:** Increased feelings of anxiety or jitteriness.
- **Headache:** Common, especially during the initial stages of treatment.
- **Gastrointestinal issues:** Nausea, stomach pain, or diarrhea [3].

### Bromocriptine

- **Nausea and vomiting:** Common, especially when starting treatment.
- **Orthostatic hypotension:** Risk of dizziness or fainting when standing up.
- **Headache:** Frequent, particularly at the beginning of treatment.
- **Fatigue:** Feeling unusually tired or weak.
- **Confusion and hallucinations:** Rare but possible, especially at higher doses.
- **Raynaud's phenomenon:** Reduced blood flow to extremities, causing fingers and toes to feel cold or numb [4].

### Levodopa/Carbidopa

- **Nausea and vomiting:** Common gastrointestinal side effects.
- **Dyskinesia:** Involuntary movements, particularly with long-term use.
- **Orthostatic hypotension:** Risk of dizziness or fainting upon standing.
- **Hallucinations and confusion:** Possible, especially in older adults or at higher doses.
- **Sleep disturbances:** Insomnia or excessive daytime sleepiness.
- **Cardiovascular effects:** Monitor for changes in heart rate and blood pressure [4].

### General monitoring tips

- **Regular assessments:** Conduct regular assessments to monitor for side effects and adjust dosages as needed.
- **Patient education:** Educate patients and caregivers about potential side effects and when to seek medical attention.
- **Gradual dose adjustments:** Start with low doses and gradually increase to minimize side effects.
- **Hydration and nutrition:** Encourage adequate

hydration and nutrition to help manage gastrointestinal side effects.

- **Blood pressure monitoring:** Regularly check blood pressure, especially when initiating or adjusting doses.
- **Mental health monitoring:** Be vigilant for changes in mood, behaviour, or cognitive function [2].

### Management of side effects of Dopaminergic agents

Managing side effects effectively when using dopaminergic agents for traumatic brain injury (TBI) involves a combination of proactive monitoring, patient education, and appropriate interventions. Here are some strategies for managing common side effects:

#### 1. Nausea and Vomiting

- **Preventive measures:** Start with a low dose and gradually increase to minimize gastrointestinal upset.
- **Medications:** Consider prescribing antiemetics such as ondansetron or metoclopramide to manage nausea.
- **Dietary adjustments:** Advise patients to take medications with food to reduce stomach irritation.
- **Hydration:** Encourage adequate fluid intake to prevent dehydration.

#### 2. Dizziness and orthostatic hypotension

- **Gradual position changes:** Advise patients to rise slowly from sitting or lying positions to prevent dizziness.
- **Hydration:** Ensure patients are well-hydrated, as dehydration can exacerbate hypotension.
- **Compression stockings:** Consider using compression stockings to improve blood circulation.
- **Medication adjustment:** Consider reducing the dose or switching to an alternative agent if dizziness persists.

#### 3. Insomnia

- **Timing of medication:** Administer stimulating medications like methylphenidate earlier in the day to avoid interference with sleep.
- **Sleep hygiene:** Encourage good sleep practices, such as maintaining a regular sleep schedule and creating a restful environment.

- **Medications:** Consider prescribing a mild sedative or sleep aid for short-term use if necessary.

#### 4. Agitation and Anxiety

- **Behavioural interventions:** Implement behavioural strategies to manage agitation, such as a calm environment and structured routines.
- **Medication adjustment:** If agitation is severe, consider reducing the dose or switching to a less stimulating dopaminergic agent.
- **Anxiolytics:** In some cases, short-term use of anxiolytics like benzodiazepines may be appropriate, but use with caution due to potential side effects.

#### 5. Headaches

- **Hydration:** Ensure patients are well-hydrated, as dehydration can contribute to headaches.
- **Pain management:** Use over-the-counter pain relievers such as acetaminophen or ibuprofen as needed.
- **Medication review:** Review the medication regimen if headaches persist and consider dose adjustments or alternative treatments.

#### 6. Appetite suppression and weight loss

- **Nutritional support:** Provide dietary counselling to ensure adequate caloric intake and balanced nutrition.
- **Frequent meals:** Encourage small, frequent meals and snacks to maintain energy levels.
- **Monitor weight:** Regularly monitor weight and nutritional status and adjust the treatment plan.

#### 7. Fatigue

- **Activity scheduling:** Encourage patients to schedule activities during times of peak energy and to take regular rest breaks.
- **Medication timing:** Adjust the timing of medications to avoid exacerbating fatigue.
- **Physical therapy:** Incorporate physical therapy to improve overall stamina and energy levels.

#### 8. Confusion and hallucinations

- **Medication review:** If confusion or hallucinations occur, review the medication regimen and consider dose reduction or discontinuation.
- **Environmental modifications:** Ensure a safe and supportive environment to reduce confusion.

- **Psychiatric consultation:** In severe cases, consult a psychiatrist for further evaluation and management.

## 9. Cardiovascular effects

- **Regular monitoring:** Monitor blood pressure and heart rate regularly, especially when initiating or adjusting doses.
- **Medication adjustment:** Consider reducing the dose or switching to an alternative agent if significant cardiovascular side effects occur.
- **Lifestyle modifications:** Encourage a heart-healthy lifestyle, including regular exercise and a balanced diet.

## 10. Orthostatic hypotension

- **Severe dizziness or fainting:** Frequent or severe dizziness or fainting episodes, especially when standing up quickly.

## 11. Renal and hepatic

- **Liver dysfunction:** Symptoms include jaundice (yellowing of the skin or eyes), dark urine, severe fatigue, or abdominal swelling.
- **Kidney dysfunction:** Signs of kidney problems, such as reduced urine output, swelling in the legs or ankles, or unexplained fatigue.

## 12. Hematologic issues

- **Unusual Bleeding or Bruising:** Easy bruising, prolonged bleeding from cuts, or unusual bleeding (e.g., nosebleeds, bleeding gums).
- **Pale Skin or Fatigue:** Signs of anaemia, such as pale skin, fatigue, or shortness of breath.

## Allergic reactions

- **Anaphylaxis:** Signs of a severe allergic reaction, including difficulty breathing, swelling of the face, lips, tongue, or throat, and hives.
- **Rash or skin reactions:** Severe skin reactions, such as widespread rash, blistering, or peeling skin.

## Management of serious side effects

- **Immediate medical attention:** Any signs of serious side effects should prompt immediate medical evaluation. Patients should be advised to seek emergency care if they experience severe symptoms.
- **Medication review:** Discontinue the offending agent and consider alternative treatments. Adjust

dosages or switch to a different class of medication if necessary.

- **Supportive care:** Provide supportive care to manage symptoms, such as intravenous fluids for dehydration or medications to control seizures or blood pressure.
- **Monitoring:** Increase the frequency of monitoring for patients who have experienced serious side effects to prevent recurrence and ensure safety [4].

## Brain Injury Recovery Guidelines (BIRG) (proposed guidelines by the author)

### Patient's clinical profile

- **Severity of TBI:** Assess the severity of the brain injury (mild, moderate, severe) using tools like the Glasgow Coma Scale (GCS).
- **Specific symptoms:** Identify the primary symptoms that need to be addressed, such as cognitive deficits, motor impairments, agitation, or attention problems.
- **Medical history:** Consider the patient's overall medical history, including any pre-existing conditions, allergies, or contraindications to certain medications [4].

### Patient and family preferences

- **Patient preferences:** Consider the patient's preferences and willingness to adhere to the treatment plan.
- **Family involvement:** Involve family members in decision-making, especially if the patient has cognitive impairments [4].

### Multidisciplinary approach

- **Team collaboration:** Develop a comprehensive treatment plan with a multidisciplinary team that includes neurologists, rehabilitation specialists, pharmacists, and nurses.
- **Holistic care:** Integrate pharmacological treatment with non-pharmacological interventions, such as physical therapy, occupational therapy, and cognitive rehabilitation [4].

### Examples of agent selection based on symptoms

- **Cognitive deficits and attention problems:**
- **Amantadine:** Enhances cognitive function and attention.
- **Methylphenidate:** Improves attention and

concentration [2].

### Motor impairments

- **Levodopa/Carbidopa:** Enhances motor function.
- **Pramipexole:** Improves motor symptoms [4].
- **Agitation and behavioural issues:**
- **Amantadine:** Reduces agitation and improves cognitive function.
- **Bromocriptine:** This may help with behavioural disturbances [4].

### Fatigue and apathy

- **Methylphenidate:** Reduces fatigue and improves motivation.
- **Ropinirole:** May help with apathy and fatigue [4].

### Step-by-step approach to choosing the right agent

1. **Assess the patient:** Conduct a thorough assessment of the patient's symptoms, medical history, and overall condition.
2. **Review options:** Evaluate the available dopaminergic agents and their pharmacological properties.
3. **Consider evidence:** Look at clinical evidence and guidelines supporting using specific agents.
4. **Discuss with the team:** Collaborate with the multidisciplinary team to develop a treatment plan.
5. **Educate the patient and family:** Explain the treatment options, potential benefits, and side effects to the patient and their family.
6. **Start low, go slow:** Begin with a low dose and gradually increase based on the patient's response and tolerance.
7. **Monitor and adjust:** Regularly monitor the patient's progress and adjust the treatment plan as needed [4].

**Combination therapy:** dopaminergic agents can be used together to facilitate recovery in patients with traumatic brain injury (TBI). This approach, known as combination therapy, can potentially enhance therapeutic effects by targeting various aspects of the dopaminergic system. However, combining these agents requires careful consideration and monitoring to avoid adverse effects and interactions. Here are some key points to consider when using dopaminergic agents together:

### Potential benefits of combination therapy

- **Enhanced efficacy:** Combining agents with different mechanisms of action may provide a more comprehensive approach to improving cognitive and motor functions.
- **Targeted symptom management:** Different agents can address various symptoms simultaneously, such as using one agent for cognitive enhancement and another for motor function improvement.
- **Synergistic effects:** Some combinations may have synergistic effects, where the combined effect is greater than the sum of the individual effects [4].

### Common combinations and their uses

#### Amantadine and Methylphenidate

- **Amantadine:** Enhances dopamine release and blocks NMDA receptors, improving cognitive and motor functions.
- **Methylphenidate:** Inhibits dopamine and norepinephrine reuptake, improving attention and concentration.
- **Use:** This combination can effectively treat patients with cognitive deficits and attention problems [2].

#### Levodopa/Carbidopa and Bromocriptine

- **Levodopa/Carbidopa:** Increases dopamine levels in the brain, improving motor function.
- **Bromocriptine:** A dopamine agonist that stimulates dopamine receptors, enhancing cognitive and motor recovery.
- **Use:** This combination can be beneficial for patients with significant motor impairments and cognitive deficits [4].

#### Pramipexole and Amantadine

- **Pramipexole:** A dopamine agonist that selectively stimulates dopamine D2 and D3 receptors, improving motor and cognitive functions.
- **Amantadine:** Enhances dopamine release and blocks NMDA receptors.
- **Use:** This combination can be helpful for patients with both motor and cognitive impairments [4].

### Considerations for combination therapy

- **Start low, go slow:** Begin with low doses of each agent and gradually increase based on patient response and tolerance.



- **Monitor for interactions:** Be vigilant for potential drug interactions and additive side effects, such as increased risk of nausea, dizziness, or cardiovascular issues.
- **Regular monitoring:** Conduct regular assessments to monitor efficacy and side effects. Adjust dosages as needed based on patient progress and tolerance.
- **Patient-specific factors:** When selecting and dosing agents, consider individual patient factors such as age, weight, renal function, and comorbidities.
- **Consultation with specialists:** Develop and monitor the treatment plan by collaborating with a multidisciplinary team, including neurologists, pharmacists, and rehabilitation specialists [4].

### Example protocol for combination therapy

- **Initial assessment:** Thoroughly assess the patient's symptoms, medical history, and overall condition.
- **Selection of agents:** Choose appropriate dopaminergic agents based on the patient's specific needs and the potential benefits of combination therapy.

### Dosing schedule

- **Week 1:** Start with low doses of each agent (e.g., amantadine 100 mg once daily and methylphenidate 5 mg once daily).
- **Week 2:** Increase doses based on tolerance (e.g., amantadine 100 mg twice daily and methylphenidate 5 mg twice daily).
- **Week 3-4:** Continue to titrate doses as needed, monitoring for efficacy and side effects.
- **Regular follow-up:** Schedule follow-up visits to reassess the patient's progress and adjust the treatment plan as needed [2].

### Monitoring parameters

- **Cognitive and functional outcomes:** Use validated scales to assess improvements in cognitive and motor functions.
- **Side effects:** Monitor for common side effects such as nausea, dizziness, insomnia, and agitation. Be alert for serious side effects like severe hypertension, cardiac arrhythmias, and neuropsychiatric symptoms.

- **Vital signs:** Regularly check blood pressure and heart rate, especially when using agents that can affect cardiovascular function [4].

### Risks of Combination Therapy

- **Increased risk of side effects:** Combining dopaminergic agents can increase the risk of side effects, including nausea, vomiting, dizziness, insomnia, and agitation.
- **Cardiovascular effects:** Agents like methylphenidate and bromocriptine can increase heart rate and blood pressure, and their combined use may exacerbate these effects, leading to hypertension or arrhythmias.
- **Neuropsychiatric symptoms:** The risk of neuropsychiatric symptoms such as anxiety, agitation, hallucinations, and confusion may be higher with combination therapy [4].
- **Additive side effects:** Combining dopaminergic agents can lead to an increased risk of side effects such as nausea, vomiting, dizziness, insomnia, and agitation.
- **Cardiovascular effects:** Agents like methylphenidate and bromocriptine can increase heart rate and blood pressure, and their combined use may exacerbate these effects, leading to hypertension or arrhythmias.
- **Neuropsychiatric symptoms:** The risk of neuropsychiatric symptoms such as anxiety, agitation, hallucinations, and confusion may be higher with combination therapy.

### Drug interactions

- **Pharmacodynamic interactions:** Combining agents that act on the same or similar pathways can lead to enhanced effects, which may be beneficial but also increase the risk of adverse reactions.
- **Pharmacokinetic interactions:** One drug may affect the metabolism or excretion of another, leading to altered blood levels and increased risk of toxicity or reduced efficacy.

### Overlapping toxicities

- **Liver and kidney function:** Some dopaminergic agents can affect liver and kidney function. Using multiple agents may increase the burden on these organs, leading to potential toxicity.
- **CNS effects:** The central nervous system (CNS) effects of dopaminergic agents, such as sedation

or stimulation, can be compounded, leading to excessive CNS depression or overstimulation.

### Complexity of management

- **Dosing complexity:** Managing multiple medications with different dosing schedules can be challenging, increasing the risk of dosing errors.
- **Monitoring requirements:** Combination therapy requires more intensive monitoring to detect and manage side effects and interactions, which can be resource intensive.

### Patient adherence

- **Medication burden:** The increased number of medications can lead to decreased adherence, especially if the patient experiences multiple side effects or finds the regimen too complex.
- **Confusion and compliance:** Patients with cognitive impairments may struggle to adhere to a complex medication regimen, leading to missed doses or incorrect administration.

### Potential for reduced efficacy

- **Tolerance development:** Using multiple dopaminergic agents may lead to faster tolerance development, reducing the treatment's long-term efficacy.
- **Diminished response:** In some cases, the combined effects of multiple agents may not provide the expected synergistic benefits, leading to diminished overall response.

### Strategies to mitigate risks

- **Start low, go slow:** Begin with low doses of each agent and gradually increase based on patient response and tolerance.
- **Regular monitoring:** Conduct frequent assessments for side effects, drug interactions, and overall efficacy. Adjust dosages as needed.
- **Patient education:** Educate patients and caregivers about the potential risks and signs of serious side effects. Ensure they understand the importance of adherence and proper medication administration.
- **Simplify regimens:** Simplify the medication regimen to improve adherence and reduce the risk of errors.
- **Multidisciplinary approach:** Collaborate with a multidisciplinary team to develop and monitor the

treatment plan, ensuring comprehensive care and early detection of issues.

- **Individualized treatment:** Tailor the treatment plan to the patient's needs, considering their specific symptoms, medical history, and potential for side effects [4].

### Adjusting dosages of dopaminergic agents safely

- **Start low and go slow:** To minimize the risk of side effects, begin with the lowest effective dose of the dopaminergic agent. Increase the dose gradually, typically in small increments, to allow the patient's body to adjust and monitor for adverse reactions.
- **Regular monitoring:** Conduct regular clinical assessments to evaluate the patient's medication response, including cognitive and motor function improvements. Monitor for common side effects such as nausea, dizziness, insomnia, and agitation. Use standardized scales and patient self-reports to track these symptoms. Regularly check vital signs, especially blood pressure and heart rate, as dopaminergic agents can affect cardiovascular function [2].

### Patient and caregiver education

- **Inform about side effects:** Educate patients and caregivers about potential side effects and reporting any new or worsening symptoms.
- **Adherence:** Emphasize the importance of adhering to the prescribed dosing schedule and not making any changes without consulting the healthcare provider [4].

### Individualized dosing plans

- **Tailored adjustments:** Adjust dosages based on the patient's response, tolerance, and specific needs. Consider factors such as age, weight, renal function, and comorbidities.
- **Symptom-specific adjustments:** Focus on the primary symptoms that need to be addressed, such as cognitive deficits, motor impairments, or behavioural issues [4].

### Step-by-step dosage adjustment

- **Initial phase:** Start with a low dose and maintain it for a specified period (e.g., one week) to assess tolerance.
- **Incremental increases:** Based on patient response and side effects, increase the

dose in small increments (e.g., 5-10 mg for methylphenidate, 100 mg for amantadine) at regular intervals (e.g., weekly).

- **Maximum dose:** Do not exceed the recommended maximum dose for each agent. Consider alternative treatments or combination therapy if the maximum dose is reached without adequate improvement [2].

### Managing side effects

- **Dose reduction:** If side effects occur, consider reducing the dose to the previous level where the patient was stable.
- **Symptomatic treatment:** Use additional medications to manage side effects if necessary (e.g., antiemetics for nausea, antihypertensives for high blood pressure).
- **Alternative agents:** If side effects are intolerable, consider switching to a different dopaminergic agent with a more favourable side effect profile [4].

### Regular follow-up visits

- **Frequency:** Schedule regular follow-up visits (e.g., weekly or bi-weekly initially, then monthly) to reassess the patient's progress and make necessary adjustments.
- **Comprehensive review:** During follow-up visits, conduct a comprehensive review of all monitoring parameters, including cognitive and functional outcomes, side effects, and vital signs [2].

### Example dosage adjustment schedule

#### Amantadine

- **Week 1:** Start with 100 mg once daily.
- **Week 2:** Increase to 100 mg twice daily if tolerated.
- **Week 3:** If well tolerated, consider increasing to 200 mg in the morning and 100 mg in the evening.
- **Week 4:** If further improvement is needed and tolerated, increase to 200 mg twice daily.

#### Methylphenidate

- **Week 1:** Start with 5 mg once daily.
- **Week 2:** Increase to 5 mg twice daily if no significant side effects.
- **Week 3:** If well tolerated, increase to 10 mg in the morning and 5 mg in the afternoon.
- **Week 4:** If further improvement is needed and tolerated, increase to 10 mg twice daily.

### Example dosage adjustment schedule (continued):

#### Methylphenidate (continued)

- **Week 4:** If further improvement is needed and tolerated, increase to 10 mg twice daily.

### Documentation and communication

- **Record keeping:** Maintain detailed records of all dosage adjustments, patient responses, and any side effects.
- **Team communication:** Ensure clear communication among the multidisciplinary team to coordinate care and make informed decisions about dosage adjustments [4].

### Summary of Key Findings and Recommendations

#### Key findings

1. **Classification of DOC:** The document outlines the traditional classification of DOC into coma, vegetative state/unresponsive wakefulness syndrome (VS/UWS), and minimally conscious state (MCS), with a proposal to include Post-traumatic Confusional State (PTCS) as a fourth category.
2. **Pharmacological agents:** Dopaminergic agents such as amantadine, bromocriptine, apomorphine, and levodopa/carbidopa are highlighted for their roles in facilitating recovery. Amantadine, in particular, is supported by substantial evidence for its efficacy in improving cognitive and motor functions.
3. **Treatment protocols:** The guidelines propose specific treatment protocols for each level of the RLAS, detailing the appropriate dopaminergic agents and dosages to be used at each stage. This structured approach aims to optimize patient outcomes by aligning pharmacological interventions with the patient's recovery phase.
4. **Monitoring and adjustments:** Emphasis is placed on regular assessments and monitoring to track progress and manage side effects. The document advocates for a multidisciplinary approach to ensure comprehensive care, including physical therapy, occupational therapy, and psychological support.
5. **Combination therapy:** The potential benefits and risks of combination therapy with multiple dopaminergic agents are discussed. The

guidelines recommend starting with low doses and gradually increasing based on patient response and tolerance, with careful monitoring for interactions and side effects.

## Recommendations

- **Implementation of guidelines:** Healthcare providers should adopt these best practice guidelines to standardize the use of dopaminergic agents in DOC treatment, ensuring consistency and improving patient outcomes.
- **Multidisciplinary collaboration:** Effective implementation requires collaboration among neurologists, rehabilitation specialists, pharmacists, and other healthcare professionals to provide holistic care.

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- **Ongoing research:** Continued research is necessary to refine these guidelines and explore new pharmacological interventions that may further enhance recovery in DOC patients.

## Conclusion

The proposed guidelines represent a significant advancement in the management of disorders of consciousness. By providing a clear, evidence-based framework for the use of dopaminergic agents, these guidelines aim to improve functional outcomes, cognitive function, and overall quality of life for patients with severe brain injuries. The structured approach, combined with regular monitoring and a multidisciplinary care model, offers a comprehensive strategy to facilitate recovery and reduce mortality in this vulnerable patient population.

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