Review Article

The minimally conscious state: an analysis of current clinical trials registered in ClinicalTrials.gov

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Abstract: The minimally conscious state (MCS) is a disorder of consciousness described in recent years for patients who have behavioral responses to stimuli that do not meet the classification of chronic vegetative state (CVS) or coma. This distinction is valuable in clinical practice, as minimally conscious patients may require different treatments and may have different long-term outcomes when compared to vegetative states or coma. In this report, we analyzed the ClinicalTrials.gov database to systematically assess all clinical trials regarding MCS. The database was queried using the term "minimally conscious state" in the "condition or disease" search parameter. Of the studies identified, those that had suspended, terminated, or otherwise unknown statuses were excluded. In total, 41 studies were analyzed. The included studies were initiated between 2008 and 2020, with the majority (63%) beginning in 2015 or later. Of the primary intervention modalities included, 15 (37%) evaluated stimulation modalities such as transcranial magnetic stimulation, transcranial direct current stimulation, implantable neurostimulation, vagus nerve stimulation, focused ultrasound and median nerve stimulation. Additionally, 5 (12%) used some form of behavioral therapy. A total of 4 (10%) studies involved pharmaceutical intervention, including dopamine agonists, analgesics and sedatives. Finally, 4 (10%) studies sought to determine the validity of current diagnostic methods and systems used to assess the status of patients in MCSs. Since the definition and criteria for CVS and MCS have been established, these two conditions remain closely associated despite evidence of different patient outcomes and treatment options. Many clinical trials are underway assessing interventions with stimulation. However, the trials are lacking with respect to diagnostic methods and pharmaceutical treatment.

Keywords: Clinical trials; Coma Recovery Scale-Revised (CRS-R); minimally conscious state (MCS); transcranial direct stimulation

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Introduction

The concept of consciousness has been a controversial topic throughout its history, dating back to 1886 when Sir Victor Horsley claimed that levels of consciousness were attributed to the functionality of the cerebral cortex (1). The minimally conscious state (MCS) is a relatively new classification, developed in 2002 by Giacino *et al.* to classify patients with specific behavioral features not concordant with definitions of the chronic vegetative state (CVS) or coma (2). In short, a patient in the MCS exhibits cognitively directed behavior in a reproducible and sustained manner, indicating conscious perception of the environment (2). Importantly, MCS differs from both coma and CVS which are marked by the inability to interact with the outside world or respond to the environment (3). Coma and CVS differ in that CVS has periods of wakefulness (eyes open), while coma does not have any wakefulness (eyes closed unconsciousness) (4). Diagnostic criteria for these patients are found in *Table 1* (5).

Although diagnostic criteria have been established to distinguish MCS from other disorders of consciousness, there remains a clinical challenge in correctly diagnosing and treating minimally conscious patients among clinicians (6,7). Previous studies have reported misdiagnosis of MCS at rates as high as 37–43% (8-10). This challenge is especially pertinent as patients are mistakenly given poor prognoses, resulting in premature termination of life-sustaining care (11,12). Misdiagnosis of MCS as CVS could result in a missed opportunity for early intervention and therapy associated with improved outcomes, or even premature cessation of life sustaining therapies. Patients with MCS also experience pain and suffering, whereas patients with CVS cannot (13).

Finally, early detection of consciousness in patients with severe brain injury may be associated with improved patient outcomes, allowing clinicans to make time-sensitive decisions about life-sustaining therapies with more information about patients' conditions (14). It has been estimated by prevelance studies on MCS that 1.5 in 100,000 inhabitants could be in a MCS (15). The conditions of these patients are often associated with high social, emotional, and economic burdens. This highlights the need for improved diagnostics, management, and treatment methods.

The aim of this study is to analyze current clinical trials regarding MCS for the purpose of discovering the methodologies, current trends, and obstacles facing this field of research. We also discuss potential avenues for future clinical trials to better understand this poorly understood condition.

Methods

The analysis of current clinical trials studying MCSs was conducted using the ClinicalTrials.gov database, maintained by the National Library of Medicine at the National Institutes of Health. Information about the trial is submitted by the sponsor or lead investigator and may be updated as the study progresses. At the time of writing, this database contains >400,000 clinical trials conducted throughout the United States and in 220 countries (16).

The trials included for analysis in this report were identified using the search query "minimally conscious state" in the "condition or disease" search parameter. Of the studies identified, those that had suspended, terminated, or otherwise unknown statuses were excluded. For trials that met the inclusion criteria, the following information was tabulated: identifier number, study title, recruitment status, date of trial initiation, date of projected completion, country of trial origin, study focus, sample size, patient age range, interventions, and outcomes. For those trials that had associated results, online searches were conducted to find peer-reviewed reports.

Additionally, the search terms "coma" and "vegetative state" were also queried to compare research productivity in these areas when compared to MCSs.

Results

In total, 51 studies were identified. Of these, 10 were either suspended or of unknown status and were excluded. The remaining 41 studies were analyzed via categorial methods as follows. The 41 included studies were initiated between 2008 and 2020, with the majority (63.0%, n=26) beginning in 2015 or later (*Figure 1*). Most studies are between 1 and 3 years in length (51.2%, n=21; *Figure 2*). Notably, five trials (12.1%) studied patients or interventions for >5 years. Of the 41 trials, the median time to completion was 2.4 years.

In total, 12 countries are currently registered in the ClinicalTrials.gov database as having clinical trials studying MCS (*Figure 3*). China currently has the most clinical trials (10, 24.3%), followed by Belgium (9, 21.9%). Four studies did not have countries of origin associated with their database entry. The identified clinical trials were either interventional (28, 68.2%) or observational (13, 31.7%), with the majority (27, 65.9%) having a sample

Table 1 Previously described diagnostic criteria of MCS based from variables of the CRS-R (5)

Outcome	CRS-R score
CVS	All scores ≤2 with additional visual score ≤1 and communication score of 0
MCS	Auditory score 3–4; visual score 2–5; motor score 3–5; oromotor score 3; communication 1
Emergence from MCS	Motor score increases to 6 and communication increases to 2

CRS-R, Coma Recovery Scale-Revised; CVS, chronic vegetative state; MCS, minimally conscious state.

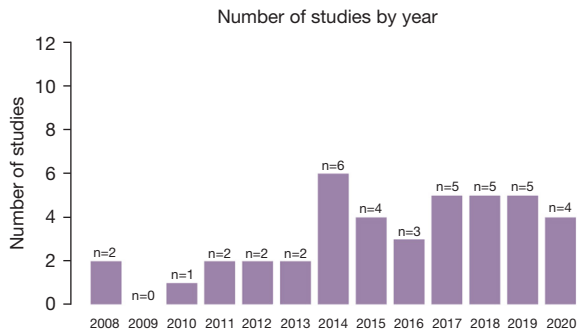

Figure 1 Bar chart depicting number of studies per year.

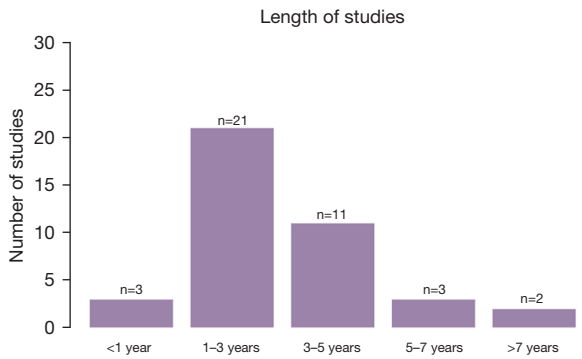

Figure 2 Bar chart depicting length of studies in years.

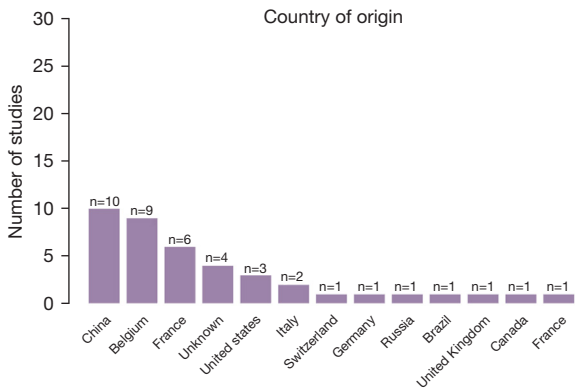

Figure 3 Bar chart depicting country of origin for each study.

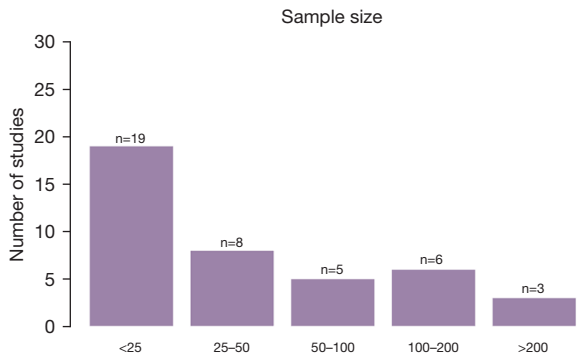

Figure 4 Bar chart depicting sample sizes of each study.

size less than 50 patients. The median number of study participants was 30 (*Figure 4*). Of the observational studies, most were prospective cohort studies (10, 77%), with only a small number being cross-sectional cohort (2, 15.4%) or prospective case-only studies (1, 8%).

The study populations of the trials generally included men and women beginning at 18 years of age with a small number also including adolescents between the age of 14 and 17. The upper bound of age ranged from 65 to 99 years, with most trials excluding participants above 75 years of age.

While all of the trials included for analysis pertain to MCS, they differ in both their focus and methods of intervention and evaluation. Of the 28 interventional studies, 15 (53.5%) used stimulation of the CNS as the primary intervention. These included transcranial magnetic stimulation, transcranial direct current stimulation (tDCS), implantable neurostimulation, vagus nerve stimulation, focused ultrasound and median nerve stimulation. Of all studies, 5 (17.8%) used some form of therapy or behavioral modification (e.g. interactions with animals, personalized objects, sounds, and odors) as stimuli, and assessed participants' physiological responses. Another 4 (14.2%)

Table 2 Table depicting criteria of the CRS-R

Auditory Function Scale
4: Consistent movement to command
3: Reproducible movement to command
2: Localization to sound
1: Auditory startle
0: None
Visual Function Scale
5: Object recognition
4: Object localization: reaching
3: Visual pursuit
2: Fixation
1: Visual startle
0: None
Motor Function Scale
6: Functional object use
5: Automatic motor response
4: Object manipulation
3: Localization to noxious stimulation
2: Flexion withdrawal
1: Abnormal posturing
0: None/floaccid
Oromotor Scale
3: Intelligible verbalization
2: Vocalization/oral movements
1: Oral reflexive movement
0: None
Communication Scale
2: Functional: accurate
1: Non-functional: intentional
0: None
Arousal Scale
3: Attention
2: Eye opening w/o stimulation
1: Eye opening with stimulation
0: Unarousable

Consciousness is scored on a total scale of 0–23 with a higher score indicating a higher level of consciousness (17). CRS-R, Coma Recovery Scale-Revised.

studies sought to determine the validity of current diagnostic methods and systems used to assess the status of patients in MCSs. Finally, 4 (14.2%) studies involved pharmaceutical intervention, including sedatives, analgesics, and dopamine agonists. Among the pharmaceuticals studied were apomorphine, dexmedetomidine, midazolam, acetaminophen, ibuprofen, diclofenac, tramadol and oxycodone.

The 13 observational studies primarily used an array of diagnostic tests to assess patients in MCS. 7 (53.8%) used a standardized form, such as the Coma Recovery Scale-Revised (CRS-R) or the Nociception Coma Scale-Revised (NCS-R). The CRS-R is a 23 point system where patients can achieve 4 points for auditory functions, 5 points for visual functions, 6 points for motor functions, 3 points for oromotor functions, 2 points for communication functions, and 3 points attributed to arousal (17). A higher score is associated with a higher level of consciousness (*Table 2*). Another 3 (23%) used multiple neuroimaging modalities to assess function and response, including fMRI and FDG-PET. Three (23%) studies did not have an evaluation method associated with their database entry.

While 25 of the 41 studies are listed as completed, only 3 of the ClinicalTrials.gov database entries have been updated with post-study reports. Furthermore, only 1 of these studies was associated with peer-reviewed literature about the results of the study.

Of these studies, NCT01673126 was completed in August, 2010. It was a phase II randomized interventional crossover clinical trial with 55 participants studying the tDCS for disorders of consciousness. Patients received tDCS for 20 minutes follow by assessment with the CRS-R with the primary endpoint being the change in CRS-R scores. It is important to note that this study did not differentiate among CVS and MCSs.

NCT00557076 assessed the efficacy on familiar voices during disorders of consciousness. This was a randomized parallel assignment interventional clinical trial with 21 patients. This found that patients had increases in CRS-R scores when given auditory stimulation of individuals well known to the patient at least 1 year before the injury. It is important to note that this study did not differentiate among CVS, coma, MCSs and traumatic brain injury patients.

NCT02025439 is a randomized interventional clinical trial with 4 participants where they compared amantadine and repetitive transcranial magnetic stimulation (rTMS) together with amantadine alone and rTMS alone for the treatment of chronic impaired consciousness. They found that patients using both modalities have a high rate of

adverse events such as fatigue, hypertension, hypotension, infection and weight loss, skin break down, skin integrity, breakdown of scalp and sweating. These were patients that experienced a traumatic brain injury at least one year prior and were in a chronic state of impaired consciousness, thus excluding patients without trauma. In addition, the sample size was small with only 4 patients limiting its conclusions.

All the three aforementioned clinical trials found 0% mortality and no serious adverse events in the cohorts.

The search search term "coma" returned 162 clinical trials that were either recruiting, active or completed. The search term "vegetative state" returned 49 studies that were either recruiting, active or completed.

Discussion

Research on disorders of consciousness has proliferated in recent years; however, an understanding of these conditions still remains elusive to neuroscientists and clinicians. This is especially evident in distinguishing MCS from CVS patients, which had been closely associated until the 21st century. The term "Persistent Vegetative State" was established in 1972 by Jennett and Plum to define the condition of patients with severe-acquired brain injury that have recovered from sleep-like coma to possess periods of wakefulness with responsiveness limited to primitive postural and reflexive movements of the limbs (18). In 1994, the Multi-Society Task Force established comprehensive criteria to accurately diagnose patients with CVS (19). However, with these criteria created issues surrounding patients with cognitive activity different from those with CVS, who consequently may have been given different allocation of resources, treatment options, and prognoses. It was not until 2002 that Giacino and colleagues developed a definition and diagnostic criteria for the "minimally conscious state" in order to distinguish patients with clear and repeated signs of awareness from patients with CVS and other serious consciousness disorders (2). This was a vital publication for this field of research, as patients diagnosed with MCS have been documented to show more continuous improvement and attain more favorable long-term outcomes than those in CVS (20).

As MCS is a somewhat novel paradigm, clinical trials on the subject have only begun in the past decade, and in lesser numbers than its more established disorders of consciousness such as CVS and coma. As previously mentioned, the rate of misdiagnosis of MCS can be as high as 43% (9). With only 41 studies being registered on ClinicalTrials.gov for MCS, it is likely that many trials evaluating CVS or comma have misclassified patients and included patients in their study with MCS. The definition of MCS is now 20 years old, therefore designing a trial that does not distinguish MCS from CVS is a poorly designed trial, since these disorders have very different prognoses. MCS is also ten times more common than CVS, thus its study is even more important.

Despite the potential misclassification of trials or patients, it is clear that the number of clinical trials studying MCS is trending upwards in recent years. Most trials (62%) began in 2015 or later, with over 10 beginning in the past 2 years. It is important to consider that it has been described that the overall number of trials published in the ClinicalTrials.gov database have been increasing over the past two decades. Therefore, the uptrend in these registered studies could be the result of clinicians and scientists having a higher rate of clinical trial registration as opposed before the past two decades when the online database was not readily available or well known (Kurtz *et al.*, unpublished work). There remains a paucity of research on MCS when compared to CVS and coma. Evidence for this is noted with the search term "coma" returning 162 clinical trials while the search term "vegetative state" returned 49 studies.

Other important parameters studied in this analysis were the study length and sample size. The majority of trials (58.5%) lasted 3 years or less, with only a handful lasting more than 5 years (12.2%). Additionally, most trials had relatively small sample sizes, with a median of 30 participants. These qualities may be attributed to two factors. Firstly, as a new field of study, MCSs may not yet warrant the same degree of resource investment to sponsors as more established fields of study. Long-term trials with many participants are a strain on institutions and investigators, but can often provide important information on outcomes especially in disorders of consciousness. Secondly, finding suitable patients is likely an obstacle. Patients must be at the appropriate level of consciousness while additionally be selected to participate in a clinical trial; both of which significantly reduce the patient size available to undergo assessment.

Various approaches are explored in this series of trials, with interventions ranging from combined drug-neurostimulation regimens to therapy involving trained animals. Thus, numerous trials seek to determine the efficacy of both invasive and non-invasive interventions on outcomes in patients in MCSs. Notably, of the studies listed on ClinicalTrials.gov, 15 (36.5%) study the effects of

tDCS or another form of electrical stimulation (vagus nerve, spinal cord) on recovery from disorders of consciousness. These studies most commonly employ the CRS-R as assessments tools, as well as various physiological responses such as heart rate and heart rate variability, sweat, and EEG monitoring. While neurostimulation has been shown to enhance cortical excitability, the therapeutic effect of this method of stimulation on patient outcomes has not yet been established. Pharmaceutical interventions included mainly dopamine promotors, analgesics and sedatives. The dopamine promotor being tested is apomorphine which is thought to improve behavioral effects in patients with MCSs. Analgesics were also studied to assess the relationship of analgesic potency with NCS-R scores in patients with MCSs. This trial is evaluating whether opiate pain control improves NCS-R scores more than pain control with NSAIDs or acetaminophen. Sedatives are being evaluated including dexmedetomidine and midazolam. These are being evaluated for their use in regional anesthesia.

An additional area of focus is the diagnosis and classification of MCS. Currently, diagnosis of the state is based primarily on a subjective assessment of the patient's behavioral responses, which has been previously associated with higher rates of misdiagnosis than standardized assessments such as the CRS-R (5). As a result, many of the observational trials seek more accurate and robust methods of diagnosis. Fine-tuning and validation of the CRS-R is a shared goal of many of the observational trials (80%) and may result in novel methods of assessing neurological function. Other observational studies look to neuroimaging or electrophysiological changes as diagnostic criteria and aim to differentiate patients with disorders of consciousness based on more objective measures. As the concept of MCS is still in relative nascensy, robust and valid methods of diagnosis are critical in both the treatment of these patients as well as in facilitating further research.

While more than half (60.9%) of the studies are listed as completed, only 1 is associated with results published in peer-reviewed journals (study identifier: NCT02025439). This may be due to unfavorable results, delay on the part of the investigators, or simply an artifact of un-updated entries on ClinicalTrials.gov. Nonetheless, a concerted effort should be made within the neurosurgical community to encourage the timely publishing of the results of all clinical trials.

Limitations

While assessments of clinical trials are an extremely valuable weathervane for the quality and direction of current research, they may lack robustness in that they are not validated beyond theory. That is, an analysis of clinical trials such as this one can only assess intended characteristics – not functional outcomes or parameters. In order to properly assess research directions, peer-reviewed literature is necessary. As more studies reach completion and publish data, it is likely that these can be tabulated in order for meta-analyses on various aspects of MCS to be performed.

Conclusions

Since the definition and criteria for CVS and MCS have been established, these two conditions remain closely associated despite evidence of different patient outcomes and treatment options. This report was conducted to establish the trends, methodologies and obstacles of research regarding MCS. A majority of studies are currently conducted in China and Belgium, highlighting that this field is unexplored in other countries, despite a vast number of patients classified as "minimally conscious". Furthermore, a majority of these clinical trials have small sample sizes and short study length; although this issue is attributed to financial burden and appropriate subject selection, larger and longer-term studies will provide a comprehensive scope into patient outcomes. This is important since MCS is a condition with no clear timeline, and variably little improvement with current treatments. This analysis was dominated by interventional studies, with a wide array of methods including transcranial direct stimulation, animal-assisted therapy, and behavioral modification as stimuli. However, these trials were largely lacking in diagnostic methods and pharmaceutical treatment. Diagnostic methods research is especially urgent, given the high rate of misdiagnosis for MCS. These and future studies will further highlight the need for establishing more standardized methods of diagnosis, where clinical consensus has proved to be difficult and inaccurate. Although our understanding of the MCS is still in its infancy, this field of research has many potential opportunities and is likely to continue growing with the development of new technologies and diagnostic methods.

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Footnote

Peer Review File: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-133/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-133/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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