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Pharmacologic Neurostimulation During Acute Hospitalization for Moderate-to-Severe Traumatic Brain Injury: A Systematic Review and Meta-analysis of Comparative Evidence.

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Abstract

Background

Several neurostimulants agents have been used are used off-label after traumatic brain injury (TBI), but their effectiveness during acute hospitalization remains uncertain.

Methods

We reviewed randomized and nonrandomized comparative studies of amantadine, methylphenidate, modafinil, zolpidem, or combinations in adults with moderate-to-severe TBI treated during the index ICU or hospital admission. Randomized and observational evidence were synthesized separately using random-effects models with restricted maximum likelihood and Hartung–Knapp confidence intervals. Certainty was assessed with GRADE. Uncontrolled pre–post studies were used only for narrative context. Post hoc Holm adjustment was applied within clinical domains and globally across 27 exploratory tests.

Results

Thirteen studies were included; 10 contributed to meta-analysis. Neurostimulants were not associated with clear differences in GCS at the first post-treatment assessment between days 7 and 11 (MD, 1.91; 95% CI, − 0.55 to 4.37), discharge GCS (MD, 0.03; 95% CI, − 1.03 to 1.10), in-hospital mortality (RR, 0.65; 95% CI, 0.27–1.53), 6-month functional outcome (SMD, 0.06; 95% CI, − 4.98 to 5.10), ICU length of stay (RoM, 0.96; 95% CI, 0.85–1.08), mechanical ventilation duration (RoM, 0.95; 95% CI, 0.79–1.14), or seizures (RR, 0.96; 95% CI, 0.005–182.93). After global Holm adjustment, only three common-effect observational analyses remained significant; none was reproduced by prespecified random-effects models. Certainty ranged from moderate to very low.

Conclusions

Comparative evidence does not establish that acute neurostimulant therapy improves consciousness or major outcomes after moderate-to-severe TBI. Apparent benefits in uncontrolled or secondary analyses may reflect spontaneous recovery, confounding, model dependence, or multiplicity. Routine acute use is not supported; adequately powered agent-specific trials are needed.

1. Introduction

Traumatic brain injury (TBI) frequently impairs arousal and consciousness during acute hospitalization, particularly after moderate-to-severe injury (1). Serial neurological examination is central to clinical monitoring, and the Glasgow Coma Scale (GCS) remains the most widely used bedside measure of

consciousness and initial injury severity (2–4). However, GCS scores may be influenced by endotracheal intubation, sedative and analgesic exposure, observer variability, extracranial complications, and examination timing (2,3,5). Neurological status may also improve during early critical care because of spontaneous recovery, resolution of secondary insults, withdrawal of sedation, surgery, and other concurrent interventions (1,2). Therefore, within-patient improvement alone cannot establish a pharmacological treatment effect.

Several agents have been used off-label to promote arousal or neurological recovery after TBI (6,7). Amantadine has dopaminergic and N-methyl-D-aspartate receptor–antagonist activity (6,8), whereas methylphenidate increases synaptic dopamine and norepinephrine through transporter inhibition (9). Modafinil is an atypical wake-promoting agent that inhibits the dopamine transporter and modulates catecholaminergic and arousal-related networks (10). Zolpidem differs mechanistically because it is a sedative-hypnotic with preferential activity at α1-containing γ-aminobutyric acid type A receptors. Nevertheless, paradoxical improvements in arousal and behavior have been reported in a small minority of patients with disorders of consciousness, supporting its investigation despite its distinct mechanism (6).

The strongest comparative evidence for pharmacological stimulation after TBI derives from the postacute rehabilitation setting (6,11). In a landmark randomized trial of patients with vegetative or minimally conscious states 4–16 weeks after injury, amantadine accelerated functional recovery during active treatment, although cumulative improvement was similar between groups after treatment withdrawal (11). Because these patients were medically stable and receiving inpatient rehabilitation, these findings are not directly generalizable to treatment initiated during the index ICU or hospital admission.

Studies conducted during acute hospitalization have generally been small and heterogeneous in injury severity, treatment timing, drug selection, outcome definitions, and follow-up duration (7,12–15). Previous reviews have often combined acute and postacute populations, different study designs, and outcomes assessed at varying time points, sometimes discussing uncontrolled pre–post findings alongside comparative evidence (6,16). This limits phase-specific and causal interpretation. For this review, acute hospitalization was defined as the index ICU or hospital admission after injury, before transfer to dedicated inpatient rehabilitation, with treatment initiated during that admission.

We therefore conducted a systematic review and meta-analysis of comparative studies evaluating amantadine, methylphenidate, modafinil, and zolpidem, alone or in combination, in adults hospitalized with moderate-to-severe TBI.

2. Materials and Methods

2.1 Study design and registration

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement. The protocol was prospectively registered in PROSPERO (CRD420261325880).

2.2 Eligibility criteria

We included randomized controlled trials and prospective or retrospective comparative cohort studies enrolling adults with moderate-to-severe TBI, defined as an admission GCS score ≤ 12 or an equivalent clinical or anatomical criterion used by the original investigators. Studies with unclear severity definitions or predominantly adult populations that included a small proportion of participants younger than 18 years were retained conditionally and evaluated in sensitivity analyses.

TBI severity was classified at the study level as moderate, severe, mixed moderate-to-severe, or unstratified according to the investigators' reported criteria. Severity-stratified meta-analysis was planned when outcomes were reported separately; however, most studies enrolled predominantly severe TBI, included mixed populations without subgroup-specific data, or reported only aggregate baseline GCS values. We therefore did not derive separate estimates for moderate and severe TBI or assign studies to severity categories based solely on mean or median GCS, which could misclassify mixed cohorts and introduce ecological bias.

Acute hospitalization was defined as the index ICU or hospital admission after injury, before transfer to dedicated inpatient rehabilitation, with treatment initiated during that admission. Studies conducted exclusively in rehabilitation, outpatient, subacute, or chronic disorders-of-consciousness settings were excluded.

Eligible interventions were amantadine, methylphenidate, modafinil, zolpidem, or combinations of these agents, compared with placebo, standard care, or another eligible intervention. Combination regimens were analyzed separately. These agents were prespecified because they had been evaluated clinically for arousal or consciousness recovery after TBI and were the drugs most frequently identified in the acute-hospital literature during preliminary scoping. Other agents, including dextroamphetamine, bromocriptine, levodopa, and ropinirole, were outside the predefined scope; their exclusion should not be interpreted as evidence of ineffectiveness.

We excluded studies without a concurrent comparator, mixed neurological cohorts without separable TBI data, case reports, uncontrolled case series, reviews, protocols, conference abstracts with insufficient data, and nonhuman studies. Clinically relevant uncontrolled studies were considered only for narrative context and were not used to estimate treatment efficacy.

2.3 Search strategy and study selection

PubMed/MEDLINE, Embase, Scopus, and Web of Science were searched from inception through March 2026. Controlled vocabulary and free-text terms related to traumatic brain injury, disorders of consciousness, amantadine, methylphenidate, modafinil, zolpidem, and neurostimulant therapy were

combined using database-specific syntax. Reference lists of eligible studies and relevant reviews were also screened. Complete search strategies are provided in **Supplementary Material 1.**

Records were deduplicated in Zotero and screened in Rayyan. Two reviewers independently assessed titles and abstracts and subsequently evaluated potentially eligible full-text reports. Disagreements were resolved by consensus or, when necessary, by a third reviewer. Reasons for full-text exclusion were documented in the PRISMA flow diagram.

2.4 Data extraction and outcomes

Two reviewers independently extracted data using a standardized form. Variables included study design, population and injury characteristics, baseline neurological status, sedation and analgesic exposure, intubation and mechanical ventilation, neurosurgical procedures, intervention dose and timing, comparator characteristics, outcome definitions and assessment times, effect estimates, denominators, adverse events, and treatment discontinuations.

For randomized trials, we extracted arm-level means, standard deviations, event counts, and analyzed denominators. For observational studies, adjusted estimates were preferred when available. Shared control groups, repeated assessments, multiple intervention arms, and multiple outcomes derived from the same participants were identified prospectively to prevent double-counting. The prespecified outcome domains were:

- **Recovery of consciousness**, primarily assessed using the GCS at the first prespecified post-treatment evaluation between days 7 and 11 after treatment initiation or randomization. Assessments at discharge, treatment completion, washout, or later follow-up were analyzed separately.
- **Mortality**, classified by assessment period as ICU, in-hospital, or longer-term.
- **Global functional outcome**, measured using the Glasgow Outcome Scale, Glasgow Outcome Scale–Extended, Disability Rating Scale, or another validated instrument.
- **Healthcare utilization**, including ICU and hospital length of stay, duration of mechanical ventilation, ventilator-free days, and tracheostomy.
- **Safety**, including seizures, cardiovascular or laboratory abnormalities, serious adverse events, and treatment discontinuation.

Repeated time points were not treated as independent observations. ICU and total hospital length of stay were analyzed separately, and mortality outcomes from different follow-up periods were not pooled indiscriminately.

Because GCS may be influenced by factors other than consciousness recovery, we also extracted the reporting of sedation or analgesia, intubation and ventilation status, conditions under which neurological examinations were performed, neurosurgical interventions, extracranial injuries, and the type and anatomical distribution of intracranial lesions. These variables were classified as reported, partially

reported, or not reported, without imputation of missing study-level data. As they were inconsistently defined and rarely available by treatment arm or outcome, they were summarized descriptively and were not incorporated into pooled adjusted analyses.

2.5 Risk of bias and certainty of evidence

Two reviewers independently assessed randomized trials using the Cochrane Risk of Bias 2 tool and nonrandomized comparative studies using ROBINS-I. Assessments were outcome-specific when appropriate. For observational studies, particular attention was given to confounding by indication, neurological severity, sedation, mechanical ventilation, neurosurgical procedures, treatment timing, survivor bias, and immortal-time bias. Disagreements were resolved by consensus or third-reviewer adjudication.

Studies at critical risk of bias were excluded from the primary treatment-effect estimates and retained only in clearly labeled sensitivity or exploratory analyses.

The certainty of evidence for the principal outcomes was evaluated using GRADE, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias. Randomized and nonrandomized evidence were evaluated separately. Certainty was classified as high, moderate, low, or very low, and reasons for downgrading were documented in Summary of Findings tables.

2.6 Statistical analysis

Continuous outcomes measured on the same scale were summarized as mean differences (MDs) with 95% confidence intervals (CIs); standardized mean differences were used for conceptually comparable outcomes measured with different instruments. Binary and time-to-event outcomes were summarized as risk ratios and hazard ratios, respectively.

Ratios of means were used as the primary effect measure for ICU length of stay, hospital length of stay, and duration of mechanical ventilation to account for differences in baseline durations across studies; absolute MDs were examined in sensitivity analyses. When results were reported as medians and interquartile ranges, means and standard deviations were estimated using the methods of Wan et al. and Luo et al. (17,18). These conversions were applied to ICU stay, hospital stay, and mechanical ventilation duration in one study (19), corresponding to six arm-level estimates. Sensitivity analyses excluded all converted data.

Randomized and observational studies were synthesized separately, and combination regimens were not attributed to either individual drug. Random-effects models were prespecified because of anticipated clinical heterogeneity and fitted using restricted maximum likelihood with Hartung–Knapp CIs. Common-effect models were examined as sensitivity analyses. Multi-arm models accounting for correlated estimates were used when treatment groups shared a comparator, thereby avoiding duplicate inclusion of control participants.

Heterogeneity was evaluated using τ^2, I^2, and Cochran's Q alongside clinical and methodological differences. Sensitivity analyses assessed the influence of study design, risk of bias, uncertain adult or TBI-severity eligibility, combination therapy, converted data, outcome timing, and effect-measure selection.

Meta-regression was planned to explore treatment timing, dose, baseline TBI severity or consciousness, sedation exposure, and study design when at least 10 independent studies and sufficient covariate variation were available. No outcome met these criteria; therefore, meta-regression was not performed because estimates would have been unstable and vulnerable to spurious or ecological associations.

A post hoc multiplicity analysis was conducted across secondary, subgroup, common-effect, and sensitivity analyses that tested associations between neurostimulant therapy and clinical outcomes. Treatment-effect tests were grouped into five clinically defined domains: consciousness, mortality, global functional outcome, healthcare utilization, and safety. Nominal p values were adjusted using the Holm procedure both within each clinical domain and globally across all eligible exploratory tests. The Benjamini–Hochberg procedure was additionally applied as a sensitivity analysis.

Tests of heterogeneity, model diagnostics, baseline characteristics, and other analyses not directly evaluating treatment benefit or harm were excluded from the multiplicity families. Leave-one-out analyses resulting in a single remaining study were also excluded because they did not provide a comparable pooled hypothesis test. Because the multiplicity analysis was post hoc, adjusted findings were considered supportive and did not replace the prespecified random-effects analyses.

Primary interpretation was based on prespecified random-effects analyses, whereas subgroup, common-effect, and sensitivity analyses were considered exploratory. Isolated nominally significant findings were interpreted cautiously, particularly when not reproduced across analyses. Funnel plots and formal asymmetry tests were planned only for outcomes with at least 10 independent studies. All tests were two-sided, and analyses were performed in R using the *meta, metafor*, and *dplyr* packages.

3. Results

3.1 Study selection

The initial search across four databases yielded 1207 records. After removing 434 duplicates, 773 unique records were screened by title and abstract. Of these, 42 were sought for full-text review. Among these, 29 articles were excluded (8 due to lack of full-text availability (4), DOI (2) or article not found (2), 9 because they were case reports, posters or clinical trial protocols, 10 that included non-TBI patients and evaluated patients on subacute or chronic TBI period and 2 given that they do not specify day of neurostimulant administration). Ultimately, 13 studies met the inclusion criteria for the systematic review (12,14,19–29), of which 10 (12,14,19,20,22,24–26,28,29) provided sufficient data for quantitative synthesis in the meta-analysis. The selection process is summarized in Fig. 1 (30).

Figure 1. **PRISMA 2020 flow diagram for study selection.**

3.2 Characteristics of included studies

Thirteen studies were included: eight randomized placebo-controlled trials and five retrospective comparative studies. Sample sizes ranged from 40 to 404 participants, mean ages from 29.35 to 48.33 years, and the proportion of male participants from 56.66% to 92.5%. Studies were conducted in Slovakia (20), Iran (12,14,19,24–28), the United States (21–23), and Turkey (29). Amantadine was the most frequently evaluated agent, followed by modafinil, methylphenidate, and zolpidem. Treatment was initiated within the first 2 weeks after TBI in all studies, whereas follow-up ranged from the first hospital day to 1 year after discharge. Study characteristics are summarized in Table 1.

Reporting of factors that could influence consciousness assessment was incomplete and heterogeneous. Sedation or sedative exposure was addressed in seven studies, often only as an exclusion criterion, protocolized practice, or medication exposure without dose or duration data. Intubation or mechanical ventilation was reported in eight studies, although the timing of neurological examination relative to ventilation and sedation was seldom specified. Neurosurgical procedures were reported, analyzed, or used as exclusion criteria in eight studies. Extracranial injuries were addressed in five studies, generally through exclusion of multiple trauma, spinal cord injury, or injuries that could interfere with neurological assessment. Eight studies provided at least partial information on intracranial injury type or distribution, ranging from broad diagnostic categories to detailed computed tomography findings.

Six studies enrolled exclusively patients with severe TBI, generally defined by an admission GCS of 3–8 or ≤ 8. Four included mixed moderate-to-severe populations that were predominantly severe, one enrolled a study-defined moderate TBI population, one explicitly included moderate and severe strata, and one reported no severity threshold but had baseline GCS values compatible with a mixed population. Although one study reported the numbers of moderate and severe cases, none of the mixed cohorts provided outcome data separately by severity; therefore, severity-stratified meta-analysis was not feasible (12,20,21,25,26,29).

Consciousness was evaluated using the GCS alone in 10 studies (12,19–26,28) and both the GCS and Full Outline of UnResponsiveness score in three (14,27,29). Mortality was reported in 12 studies, predominantly during ICU or hospital admission; only one study extended mortality follow-up to 6 months after discharge (12,14,19–22,24–29). Seven studies assessed functional outcomes using the GOSE, DRS, Disability Motor Score, MMSE, or KPS (12,14,19,21,24–26).

Nine studies reported length of stay: four separately reported ICU and total hospital stay (19,22,24,28), three reported ICU stay only (12,20,25), one reported hospital stay only (14), and one did not distinguish between ICU and total hospitalization (21). Six studies reported safety outcomes (14,19,21,22,28,29). Seizures were assessed in all six; other variably reported events included cardiovascular abnormalities, agitation, delirium, sleep–wake disturbances, gastrointestinal symptoms, hepatic or renal dysfunction,

and tracheostomy or ventilation-related outcomes. Because definitions and reporting were inconsistent, safety findings were summarized descriptively.One study reported ICU stay, hospital stay, and mechanical ventilation duration as medians and interquartile ranges (19).

Table 1. Characteristics of Included Studies Assessing The Use of Neurostimulants on Acute Moderate-Severe Traumatic Brain Injury.

3.3 Risk of bias assessment

3.3.1 Observational studies

Risk of bias in the five nonrandomized studies was assessed using ROBINS-I (Fig. 2A). Two studies were judged to be at low overall risk of bias (21,23) two at moderate risk (22,29), and one at critical risk (20).

All studies were judged to be at low risk in the domains related to participant selection, classification of interventions, deviations from intended interventions, missing data, and outcome measurement. The main concerns arose from confounding and selection of the reported result. (20) was rated at critical risk because of uncontrolled confounding, whereas (29) was rated at moderate risk in the confounding domain. (22) was judged to be at moderate risk for selection of the reported result. Overall, the principal limitations of the observational evidence were residual confounding and selective reporting, particularly in studies with nonrandom treatment allocation.

3.3.2 Randomized controlled trials

Risk of bias in the eight randomized controlled trials was assessed using the Cochrane RoB 2 tool (Fig. 2B). Four trials were judged to be at low overall risk of bias (12,19,24,26), one raised some concerns (25), and three were rated at high risk (14,27,28).

All randomized trials were judged to be at low risk in the domains of deviations from intended interventions and selection of the reported result. Limitations in the randomization process were identified in (27), which raised some concerns, and in (28), which was rated at high risk. High risk due to missing outcome data was identified in two studies (14,25), whereas one study raised some concerns regarding outcome measurement (27). Accordingly, the high overall risk-of-bias judgments were driven primarily by limitations in randomization and incomplete outcome data.

Figure 2. **Risk of bias assessment.**

3.4 Quantitative synthesis

3.4.1 Recovery of consciousness

3.4.1.1 Glasgow Coma Scale at the first post-treatment assessment

Two randomized controlled trials, comprising three active-treatment comparisons, reported GCS at the first prespecified post-treatment assessment, obtained on day 7 in one trial and day 11 in the other (Fig. 3B). Because Shafiee et al. included two intervention arms sharing a common placebo group, a multi-arm random-effects model was used to account for the correlation between comparisons. Neurostimulant therapy was not associated with a clear between-group difference in GCS during the day 7–11 assessment window (MD, 1.91 points; 95% CI, − 0.55 to 4.37; p = 0.079).

3.4.1.2 Glasgow Coma Scale at discharge

Two randomized controlled trials were included in the meta-analysis of GCS at hospital or ICU discharge (Fig. 3A). Using a random-effects model estimated by restricted maximum likelihood with the Hartung–Knapp adjustment, neurostimulant therapy was not associated with a significant difference in discharge GCS compared with the control intervention (MD, 0.03 points; 95% CI, − 1.03 to 1.10; p = 0.756). No statistical heterogeneity was detected between studies ($\tau^2 = 0$; $I^2 = 0\%$; heterogeneity p = 0.604). A common-effect model produced a concordant result (MD, 0.03 points; 95% CI, − 0.28 to 0.35; p = 0.835).

3.4.2 Mortality

3.4.2.1 In-hospital mortality in randomized controlled trials

The meta-analysis of in-hospital mortality showed no statistically significant difference between neurostimulant therapy and the control intervention (Fig. 3C). Under the random-effects model estimated using restricted maximum likelihood with the Hartung–Knapp adjustment, the pooled risk ratio was 0.65 (95% CI, 0.27–1.53; p = 0.323). No between-study heterogeneity was detected ($\tau^2 = 0$; $I^2 = 0\%$; heterogeneity p = 0.931). The common-effect Mantel–Haenszel model yielded a similar estimate (RR, 0.64; 95% CI, 0.27–1.50; p = 0.304).

3.4.2.2 Mortality during follow-up

Two studies were included in the exploratory analysis of all-cause mortality during the reported follow-up period (Fig. 4G). The random-effects model showed no statistically significant association between neurostimulant therapy and mortality (RR, 0.58; 95% CI, < 0.001–23,303.59; p = 0.632). Substantial between-study heterogeneity was observed ($\tau^2 = 1.11$; $I^2 = 80.0\%$; heterogeneity p = 0.025). Although the secondary common-effect analysis suggested lower mortality with neurostimulant therapy (RR, 0.50; 95% CI, 0.25–0.99; p = 0.047), this result was not supported by the primary random-effects model and should therefore be interpreted cautiously.

3.4.2.3 ICU mortality in observational studies

Two observational studies were included in the critical-risk sensitivity analysis of ICU mortality (Fig. 4D). Under the random-effects model with the Hartung–Knapp adjustment, amantadine treatment was not significantly associated with ICU mortality (RR, 0.18; 95% CI, < 0.001–213.81; p = 0.198). Between-study heterogeneity was low to moderate and was not statistically significant ($\tau^2 = 0.19$; $I^2 = 30.0\%$;

heterogeneity p = 0.232). A secondary common-effect analysis produced a substantially more precise estimate favoring amantadine (RR, 0.17; 95% CI, 0.07–0.40; p < 0.001).

3.4.3 Global functional recovery

3.4.3.1 Global functional outcome at 6 months

Two randomized controlled trials were included in the exploratory meta-analysis of global functional outcome at six months (Fig. 4C). Under the random-effects model estimated by restricted maximum likelihood with the Hartung–Knapp adjustment, neurostimulant treatment was not associated with a significant improvement in six-month functional outcome (SMD, 0.06; 95% CI, − 4.98 to 5.10; p = 0.901). Moderate-to-substantial heterogeneity was observed ($\tau^2 = 0.23$; $I^2 = 67.5\%$), although the heterogeneity test did not reach statistical significance (p = 0.079).

A secondary common-effect analysis yielded a small effect favoring neurostimulant therapy (SMD, 0.28; 95% CI, 0.01–0.56; p = 0.045). However, this finding was not supported by the primary random-effects analysis.

3.4.4 Healthcare utilization and duration of organ support

3.4.4.1 ICU length of stay in randomized controlled trials

Three randomized controlled trials were included in the meta-analysis of ICU length of stay (Fig. 3D). Under a random-effects model estimated using restricted maximum likelihood with the Hartung–Knapp adjustment, neurostimulant therapy was not associated with a significant reduction in ICU length of stay (RoM, 0.958; 95% CI, 0.851–1.077; p = 0.471). This estimate corresponds to an approximately 4.2% shorter ICU stay in the intervention group relative to the control group. No between-study heterogeneity was detected ($\tau^2 = 0$; $I^2 = 0\%$; heterogeneity p = 0.870).

A sensitivity analysis using the mean difference produced a concordant result, with an estimated reduction of 0.70 days in ICU length of stay that was not statistically significant (MD, − 0.70 days; 95% CI, − 2.84 to 1.45; p = 0.526). No heterogeneity was observed in this analysis ($\tau^2 = 0$; $I^2 = 0\%$; heterogeneity p = 0.821). Overall, neither effect measure provided evidence that neurostimulant therapy reduced ICU length of stay.

Zand et al. (2024) was the only study contributing ICU length-of-stay data for which means and standard deviations were estimated from medians and interquartile ranges. After excluding this study, the pooled estimate remained compatible with no clear between-group difference, although precision decreased because only two trials remained (RoM, 0.936; 95% CI, 0.670–1.308; p = 0.242). No statistical heterogeneity was detected ($\tau^2 = 0$; $I^2 = 0\%$; heterogeneity p = 0.745). The corresponding mean-difference sensitivity analysis yielded a reduction of 1.08 days that was also highly imprecise and nonsignificant (MD, − 1.08 days; 95% CI, − 10.90 to 8.73; p = 0.394; $I^2 = 0\%$). Therefore, exclusion of the converted data did not materially change the interpretation of the ICU length-of-stay findings.

3.4.4.1.1 ICU length of stay with amantadine

Two observational studies were included in the exploratory analysis restricted to patients receiving amantadine (Fig. 4F). Under the primary random-effects ratio-of-means model with the Hartung–Knapp adjustment, amantadine use was associated with a numerically longer ICU stay, although the difference was not statistically significant (RoM, 1.13; 95% CI, 0.71–1.81; p = 0.187). This point estimate corresponds to an approximately 13.0% longer ICU stay among patients receiving amantadine. No statistical heterogeneity was detected ($\tau^2 = 0$; $I^2 = 0\%$; heterogeneity p = 0.524).

The sensitivity analysis based on absolute differences similarly showed no significant association under the random-effects model (MD, 1.81 days; 95% CI, − 6.49 to 10.10; p = 0.221), with no observed heterogeneity ($I^2 = 0\%$; heterogeneity p = 0.453). Secondary common-effect models suggested longer ICU stays with amantadine both on the relative scale (RoM, 1.13; 95% CI, 1.01–1.27; p = 0.035) and the absolute scale (MD, 1.81 days; 95% CI, 0.10–3.51; p = 0.038). However, these findings were not supported by the prespecified random-effects analyses.

3.4.4.2 Hospital length of stay in randomized controlled trials

Three randomized controlled trials were included in the meta-analysis of hospital length of stay (Fig. 3E). Neurostimulant therapy was not associated with a significant difference in hospital length of stay under the random-effects model (RoM, 0.932; 95% CI, 0.691–1.256; p = 0.417). The point estimate corresponded to an approximately 6.8% shorter hospital stay in the intervention group. Between-study heterogeneity was low ($\tau^2 = 0.002$; $I^2 = 20.3\%$; heterogeneity p = 0.285).

After excluding (19), for which means and standard deviations were estimated from medians and interquartile ranges, the ratio-of-means estimate approached the null and remained highly imprecise (RoM, 1.001; 95% CI, 0.410–2.442; p = 0.991). The corresponding mean-difference sensitivity analysis also remained null and imprecise (MD, 0.03 days; 95% CI, − 20.97 to 21.04; p = 0.987).

3.4.4.2.1 Hospital length of stay with amantadine

Two observational studies were included in the exploratory analysis of hospital length of stay among patients receiving amantadine (Fig. 4E). Under the primary random-effects ratio-of-means model with the Hartung–Knapp adjustment, amantadine use was associated with a numerically longer hospital stay, although the association was not statistically significant (RoM, 1.34; 95% CI, 0.14–12.66; p = 0.344). This point estimate corresponded to an approximately 34.3% longer hospitalization among amantadine-treated patients. Substantial between-study heterogeneity was observed ($\tau^2 = 0.053$ on the logarithmic scale; $I^2 = 84.8\%$; heterogeneity p = 0.010).

The secondary common-effect analysis suggested a significantly longer hospital stay with amantadine (RoM, 1.26; 95% CI, 1.12–1.43; p < 0.001). However, this result was not supported by the primary random-

effects analysis. Similarly, the random-effects sensitivity analysis using absolute differences showed a nonsignificant increase of 7.81 days (95% CI, − 52.65 to 68.27; p = 0.348; I^2 = 83.4%), whereas the common-effect model suggested an increase of 5.90 days (95% CI, 2.56–9.24; p < 0.001).

3.4.4.3 Duration of mechanical ventilation

Three randomized controlled trials were included in the meta-analysis of mechanical ventilation duration **(**Fig. 4A**)**. The primary random-effects ratio-of-means model showed no significant difference between neurostimulant therapy and the control intervention (RoM, 0.949; 95% CI, 0.791–1.137; p = 0.337). This estimate corresponded to an approximately 5.1% shorter duration of mechanical ventilation in the intervention group. No between-study heterogeneity was detected (τ^2 = 0; I^2 = 0%; heterogeneity p = 0.744).

After excluding(19), the only study contributing converted summary statistics, the estimated effect remained nonsignificant both on the relative scale (RoM, 0.875; 95% CI, 0.676–1.133; p = 0.311) and on the absolute scale (MD, − 2.85 days; 95% CI, − 8.40 to 2.70; p = 0.314).

3.4.5 Safety outcomes

3.4.5.1 Seizures

Two studies were included in the exploratory meta-analysis evaluating the occurrence of seizures during neurostimulant therapy **(**Fig. 4B**)**. Under the random-effects model estimated using restricted maximum likelihood with the Hartung–Knapp adjustment, neurostimulant treatment was not associated with a significant difference in seizure risk compared with the control intervention (RR, 0.96; 95% CI, 0.005–182.93; p = 0.943). No between-study heterogeneity was detected (τ^2 = 0; I^2 = 0%; heterogeneity p = 0.507).

The common-effect Mantel–Haenszel model yielded a concordant point estimate and similarly showed no significant association (RR, 0.96; 95% CI, 0.29–3.16; p = 0.944).

3.4.6 Multiplicity-Adjusted Analyses

Multiplicity adjustment was applied to 27 exploratory or secondary treatment-effect tests across five clinical domains **(See supplementary table S3)**. Eight analyses had nominal p values < 0.05, but only three remained significant after both domain-specific and global Holm adjustment. These were common-effect observational analyses of hospital length of stay with amantadine, expressed as a ratio of means (RoM, 1.26; 95% CI, 1.12–1.43; domain-adjusted p = 0.003; global-adjusted p = 0.005) and as a mean difference (MD, 5.90 days; 95% CI, 2.56–9.24; domain-adjusted p = 0.007; global-adjusted p = 0.013), and ICU mortality (RR, 0.17; 95% CI, 0.07–0.40; domain-adjusted p < 0.001; global-adjusted p = 0.003). Nominally significant findings for early GCS, 6-month functional outcome, mortality during follow-up, and amantadine-associated ICU length of stay did not remain significant after Holm adjustment. Benjamini–Hochberg correction identified the same three significant analyses.

3.5 Narrative synthesis of non-poolable evidence

Among randomized trials, escalation of amantadine from 100 to 200 mg twice daily in ventilated patients with diffuse axonal injury did not improve discharge GCS, GOS, duration of mechanical ventilation, hospital stay, or mortality compared with placebo. Outcomes were assessed according to extubation, neurological improvement, or death rather than at a uniform time point (12). In another trial, amantadine produced a larger unadjusted 7-day GCS change than placebo (4.00 vs 2.34 points; p = .044), but absolute day-7 GCS, 6-month function, and mortality did not differ. The variance of the change score was unavailable, and long-term analyses included only a subset of survivors (14). A 6-week escalating regimen improved DRS change relative to placebo (10.88 vs 8.04 points; p = .015), but not GOS, and the treatment of deaths in serial functional analyses was unclear (26).

In a three-arm trial, day-11 GCS was higher with amantadine than with zolpidem or placebo, whereas GOS, ventilation duration, and hospital stay did not differ (25). Repeated measurements, a shared control group, and inconsistent mortality and discharge-GCS reporting precluded inclusion of the study as originally presented. Combined amantadine–methylphenidate treatment was associated with higher mean 6-month GOSE and lower mortality than placebo, but favorable GOSE and length of stay did not differ (24). Because both drugs were administered concurrently, agent-specific effects could not be estimated.

Observational findings were also inconsistent. In a three-group cohort, GCS improvement was smaller with amantadine than with standard care and did not differ between amantadine and modafinil when measured from treatment initiation. However, the untreated group lacked an equivalent treatment-initiation baseline, and therapy began approximately 2 weeks after admission (22). In a propensity-matched study restricted to patients surviving beyond day 10, amantadine was not associated with improved survival or command following and was associated with longer hospitalization, delayed command following, and lower discharge GOSE. Interpretation was limited by matching at admission rather than treatment initiation and substantial variability in treatment timing (21).

Another retrospective cohort reported greater 7-day improvements in GCS and FOUR scores and lower ICU mortality with amantadine, but treatment allocation was nonrandomized and continuous outcomes were reported as medians with ranges (29). An earlier pilot study reported higher survivor GCS and fewer deaths with amantadine, but inconsistent denominators and exclusion of deaths from neurological analyses prevented calculation of a valid comparative estimate (20).

Methylphenidate initiated on postinjury day 2 was associated with shorter hospitalization in severe TBI (14.10 vs 18.35 days; p = .029), but not with higher discharge GCS. Variance estimates for length of stay were unavailable, and implausible baseline GCS values raised concerns regarding data reliability (28). Modafinil did not improve GCS at 196 hours in moderate TBI, although the allocation and analytical handling of 15 deaths were not reported (27). In a predominantly severe-TBI population, modafinil increased the proportion of patients reaching prespecified GCS thresholds, but mean GCS trajectory,

time to improvement, mortality, ventilation duration, and length of stay did not differ. The responder definition was study-specific, and 11 randomized participants were excluded from the analysis (19).

Uncontrolled evidence was considered contextual only. In 79 hospitalized patients, GCS increased by 0.75 points during the first 72 hours after amantadine initiation and by 2.29 points during treatment. Without a concurrent comparator, these changes could not be separated from spontaneous neurological recovery, sedative withdrawal, or concomitant care (23).

Beyond the pooled seizure analysis, safety findings were summarized descriptively because ascertainment and reporting were inconsistent. With amantadine, seizures occurred in 3/29 patients versus 2/28 placebo recipients, and hypertension in 1/29 versus 0/28 (26). In another trial, treatment-limiting laboratory abnormalities occurred in 2/19 amantadine recipients, both involving elevated liver enzymes, compared with 6/21 placebo recipients; no seizures occurred in either group (14). Reduced glomerular filtration or elevated transaminases occurred in 7/44 amantadine-treated patients, without discontinuation, and no seizures were reported in either group (29).

In a propensity-matched cohort, nausea, vomiting, hepatic abnormalities, delirium, and seizures did not differ significantly between amantadine and matched controls (21). No serious adverse effects or dose adjustments were reported with amantadine or zolpidem in the three-arm trial (25).

No serious adverse events, discontinuations, or seizures were reported with modafinil in one trial (19), whereas another provided no extractable adverse-event counts (27). Persistent tachycardia led to discontinuation in 2/94 recipients of combined amantadine–methylphenidate and 1/94 placebo recipient (24). Post-traumatic seizures occurred in 2/20 methylphenidate-treated and 3/20 placebo-treated patients in a severe-TBI subgroup (28). Several other studies did not provide extractable treatment-emergent adverse-event data (12,20,23).

3.6 Certainty of the evidence

Table 2 presents the Summary of Findings and GRADE assessments for seven clinically critical outcomes: GCS at day 7–11 and at discharge, in-hospital mortality, 6-month global functional outcome, ICU length of stay, duration of mechanical ventilation, and seizures. Secondary or exploratory outcomes, including total hospital length of stay, longer-term mortality, and observational estimates of ICU mortality and length of stay, are presented in **Supplementary Table 1** because they were predominantly informed by nonrandomized evidence, used heterogeneous assessment windows, or overlapped with outcomes included in the main table.

Certainty ranged from moderate to very low. Evidence for ICU length of stay and mechanical ventilation duration was rated as moderate after downgrading for imprecision, as confidence intervals did not exclude clinically important benefit or harm. Evidence for GCS at day 7–11 and discharge was of low certainty because of study limitations and imprecision. Evidence for in-hospital mortality, 6-month functional outcome, and seizures was of very low certainty because of serious risk of bias, small

samples or few events, wide confidence intervals, and, for functional outcome and seizures, inconsistency or heterogeneous outcome ascertainment.

Observational evidence was consistently rated as very low certainty because of residual confounding, potential immortal-time and survivor bias, heterogeneity, and imprecision. No outcome included enough independent studies to permit formal assessment of funnel-plot asymmetry.

Table 2. Summary of Findings for Pharmacological Therapy During Acute Hospitalization for Moderate-to-Severe Traumatic Brain Injury.

4. Discussion

4.1 Principal findings

This systematic review and meta-analysis found no clear evidence that amantadine, methylphenidate, modafinil, zolpidem, or eligible combination regimens initiated during acute hospitalization improve consciousness, mortality, 6-month functional outcome, ICU or hospital length of stay, duration of mechanical ventilation, or seizure risk in patients with moderate-to-severe traumatic brain injury. Estimates for ICU length of stay and mechanical ventilation suggested little or no average effect, whereas estimates for the remaining outcomes were too imprecise to exclude clinically important benefit or harm.

Certainty of evidence ranged from moderate to very low because of risk of bias, small sample sizes, few events, heterogeneous interventions and assessment periods, and wide confidence intervals. Neurological improvements reported within treated groups or in individual studies were not consistently reproduced in the prespecified comparative random-effects analyses and may reflect spontaneous recovery, withdrawal of sedation, concurrent critical care, or other time-dependent factors.

Accordingly, the available evidence does not establish the efficacy of pharmacological neurostimulation during acute TBI hospitalization. However, the imprecision and methodological limitations of the evidence also preclude a definitive conclusion that these interventions are ineffective.

4.2 Recovery of consciousness and the importance of comparative evidence

Recovery of consciousness was the outcome most directly related to the rationale for neurostimulant therapy. Across two trials, the first post-treatment assessment, performed between days 7 and 11, the estimated between-group difference was 1.91 GCS points, but the confidence interval included no effect and clinically important effects in either direction. Because assessment timing differed between studies, this estimate should not be interpreted as a uniform day-7 effect. At discharge, the between-group difference was 0.03 GCS points, suggesting little or no effect, whereas the earlier effect remains uncertain.

Neurological improvement during acute TBI may reflect spontaneous recovery, resolution of secondary insults, withdrawal of sedation or neuromuscular blockade, postoperative recovery, and concurrent critical-care interventions. Consequently, uncontrolled pre–post changes cannot establish treatment efficacy, particularly when similar improvement occurs with placebo or when a drug-specific effect cannot be isolated (23). We therefore used uncontrolled studies only to describe clinical trajectories and prioritized concurrent between-group comparisons at prespecified time points.

Change-score findings were also interpreted cautiously when affected by baseline imbalance, unavailable variance estimates, exclusion of deaths, or nonuniform assessment timing. For example, although one trial reported greater unadjusted 7-day GCS improvement with amantadine, absolute day-7 GCS and longer-term outcomes were similar between groups (14).

Interpretation is further limited by the properties of the GCS in acute neurocritical care. Intubation, sedation, paralysis, intoxication, systemic instability, and facial or ocular trauma may alter individual components independently of consciousness (31). Identical total scores may also represent different neurological response patterns and do not reliably distinguish specific disorders of consciousness (3). Small GCS differences should therefore not be assumed to indicate clinically meaningful improvements in consciousness or functional recovery.

Future trials should report individual GCS components, airway and sedation status, and standardized assessment timing. More detailed instruments, such as the Coma Recovery Scale–Revised, may provide complementary information, although their applicability during the earliest phase of critical illness requires further evaluation (32).

4.3 Mortality, functional outcome, healthcare utilization, and safety

The mortality estimate was based on only 21 deaths and was highly imprecise, remaining compatible with both substantial benefit and clinically important harm (RR, 0.65; 95% CI, 0.27–1.53). Longer-term and ICU mortality estimates were similarly uncertain. Six-month functional outcome also showed no clear between-group difference (SMD, 0.06; 95% CI, −4.98 to 5.10). Findings that reached statistical significance only under common-effect models were considered model-dependent and exploratory rather than evidence of efficacy. This interpretation is consistent with previous amantadine-specific reviews showing no consistent improvement in Disability Rating Scale or Glasgow Outcome Scale outcomes and with the limitations imposed by heterogeneous assessment timing and case mix in TBI studies (33,34).

Between-group differences in ICU length of stay, hospital length of stay, and mechanical ventilation duration were small and nonsignificant in the primary analyses. The apparently favorable length-of-stay result for combined amantadine–methylphenidate was derived from a single cohort and from ICU and total hospital stay estimates obtained from the same participants. These correlated outcomes do not provide independent confirmation, and the absolute difference of approximately 0.76 days was of uncertain clinical importance. Accordingly, the available evidence does not support assumptions of

reduced resource utilization. Observational analyses suggesting longer hospitalization with amantadine were also inconsistent across statistical models and vulnerable to confounding by indication.

Neurostimulant therapy was not clearly associated with seizure risk (RR, 0.96), but the estimate was based on only two studies and had a wide confidence interval. Although broadly consistent with previous safety reviews, it provides limited reassurance and does not exclude clinically important effects (16,35,36). Other adverse events could not be pooled because of inconsistent definitions, ascertainment, and reporting; therefore, comparative safety between agents remains uncertain (16,36,37).

4.4 Model dependence, heterogeneity, and multiplicity

Several secondary associations reached statistical significance under common-effect models but were not reproduced in the prespecified random-effects analyses, including longer-term mortality, observational ICU mortality, 6-month functional outcome, and amantadine-associated ICU or hospital length of stay. Because the included studies differed in injury severity, treatment timing, drug exposure, and concomitant care, findings dependent on the assumption of a common underlying effect were considered exploratory rather than confirmatory. This caution is particularly relevant during acute TBI, when neurological trajectories are simultaneously influenced by spontaneous recovery, sedation withdrawal, resolution of secondary injury, surgery, and other interventions (16,35–37).

The evaluation of multiple outcomes, time points, treatment comparisons, and sensitivity analyses also increased the likelihood of chance findings. Isolated nominally significant results were therefore not interpreted as evidence of benefit or harm when they were imprecise, model-dependent, or unsupported by the primary analyses.

Post hoc multiplicity adjustment further reduced support for most nominally significant secondary findings. The associations involving early GCS, 6-month functional outcome, mortality during follow-up, and amantadine-associated ICU length of stay no longer met the conventional significance threshold after Holm adjustment. Only three findings remained significant after both domain-specific and global adjustment: observational ICU mortality under a common-effect model and amantadine-associated hospital length of stay expressed as both a ratio of means and an absolute mean difference.

These remaining findings do not provide independent or confirmatory evidence of treatment effects. The two hospital length-of-stay estimates represent alternative scales of the same underlying comparison, and all three findings arose from observational evidence analyzed under common-effect assumptions but were not reproduced by the prespecified random-effects models. Their interpretation is further limited by confounding by indication, treatment-selection and survivor biases, risk-of-bias concerns, and, for hospital length of stay, substantial between-study heterogeneity. The multiplicity analysis therefore reinforces the conclusion that isolated nominal or adjusted significance in secondary analyses should not override the null or highly imprecise primary findings.

The small number of studies precluded reliable subgroup analysis and meta-regression. Although injury severity, baseline consciousness, treatment timing, dose, sedation exposure, and study design are plausible effect modifiers, the available aggregate data could not determine whether observed heterogeneity reflected true effect modification, random variation, or ecological bias (16,35–37).

Overall, the findings are consistent with the broader literature, which supports amantadine more strongly in selected patients with postacute disorders of consciousness than during acute hospitalization after TBI (16,33,35,36).

4.5 Comparison with postacute evidence

The absence of a clear benefit during acute hospitalization does not contradict evidence supporting amantadine in selected patients with postacute traumatic disorders of consciousness. These settings represent distinct clinical contexts. The strongest evidence derives from medically stable patients treated 4–16 weeks after injury in structured rehabilitation, whereas consciousness during acute hospitalization is influenced by spontaneous recovery, secondary injury, sedation withdrawal, surgery, and other critical-care interventions that complicate causal assessment (16,35–37).

Postacute studies suggest that amantadine may accelerate recovery during active treatment in selected survivors with persistent disorders of consciousness, without establishing a sustained long-term advantage after discontinuation (35,37). In contrast, acute studies enrolled broader, more heterogeneous populations with less stable neurological trajectories and greater potential for confounding (16,33,35–37). Therefore, the present findings indicate uncertainty regarding neurostimulant use during acute hospitalization and should not be extrapolated to appropriately selected patients in postacute rehabilitation.

4.6 Risk of bias and certainty of evidence

Methodological limitations substantially reduced confidence in the effect estimates. RoB 2 identified concerns in randomized trials, particularly regarding randomization and missing outcome data, whereas ROBINS-I indicated serious confounding and treatment-selection bias in observational studies. During acute TBI care, neurostimulant initiation may depend on injury severity, sedation, mechanical ventilation, survival, and preceding neurological trajectory. Observational associations may therefore reflect prognosis, treatment indication, or survivor bias rather than pharmacological effects. Conversely, the small randomized trials lacked sufficient precision to exclude modest benefit or harm.

GRADE certainty was moderate for ICU length of stay and mechanical ventilation duration, low for consciousness outcomes, and very low for mortality, 6-month functional outcome, and seizures. Downgrading was driven primarily by risk of bias, small samples, few events, inconsistency, and wide confidence intervals. Accordingly, nonsignificant primary findings indicate insufficient evidence of benefit rather than definitive evidence of no effect, whereas isolated favorable findings from secondary or observational analyses should not be considered reliable evidence of efficacy.

Overall, uncertainty arises from limitations in study design, patient selection, treatment timing, outcome assessment, and control of time-dependent clinical confounders. This interpretation is consistent with the broader TBI neurostimulant literature, in which biological plausibility and selected favorable findings have not translated into consistent evidence of benefit during acute hospitalization (16,33,35–37).

4.7 Clinical implications

Current evidence does not support routine use of amantadine, methylphenidate, modafinil, zolpidem, or combination regimens as established therapies to improve consciousness or major clinical outcomes during acute hospitalization for moderate-to-severe TBI. Comparative benefits were not consistently demonstrated, and certainty was low or very low for most patient-important outcomes. Nevertheless, the available evidence remains insufficient to exclude benefit or harm from specific agents, treatment windows, or selected patient subgroups.

These findings should not be extrapolated to the postacute indication for amantadine. In patients with traumatic vegetative or minimally conscious states 4–16 weeks after injury, amantadine accelerated functional recovery during active treatment, supporting guideline recommendations of 100–200 mg twice daily in this selected population (11,32). Acute ICU patients differ substantially because consciousness is simultaneously influenced by sedation, secondary brain injury, surgery, organ support, and systemic complications.

When considered during acute hospitalization, neurostimulant therapy should therefore be regarded as off-label and individualized. Reversible causes of impaired consciousness—including sedative exposure, seizures, hydrocephalus, mass effect, metabolic disturbances, infection, hypoxemia, and hemodynamic instability—should be addressed first. Drug selection should account for renal and hepatic function, cardiovascular and seizure risk, concomitant medications, interactions, and agent-specific pharmacology. Zolpidem should not be considered interchangeable with conventional neurostimulants because its proposed paradoxical effect is mechanistically distinct.

Any therapeutic trial should prespecify the agent, dose, timing, objective, duration, and criteria for continuation or discontinuation. Neurological assessments should be standardized and performed under comparable sedation and ventilatory conditions whenever feasible. Observed improvement should be interpreted against the expected clinical course and concurrent interventions rather than attributed automatically to treatment.

Available data do not support preferential selection of one agent or combination therapy. Until more reliable comparative evidence is available, acute use should remain cautious, closely monitored, and preferably conducted within prospective registries or clinical trials.

4.8 Implications for future research

Future studies should use adequately powered, multicenter randomized designs with standardized definitions of treatment timing, agent, dose, titration, and duration. Randomization should occur as close

as possible to treatment initiation, and analyses should account for injury severity, baseline consciousness, sedation, mechanical ventilation, and time-dependent biases related to survival and treatment eligibility. Combination regimens should be evaluated separately from single-agent therapies.

Consciousness should be assessed at prespecified, clinically meaningful time points using absolute scores and longitudinal changes in GCS and, when feasible, the Coma Recovery Scale–Revised. Studies should report paired baseline and follow-up data with measures of variance and standardize definitions of mortality, functional outcome, ventilation duration, and healthcare utilization.

Prespecified analyses should evaluate plausible effect modifiers, including injury severity, neurological phenotype, treatment timing, and sedation exposure. These methodological improvements are required to distinguish pharmacological effects from spontaneous recovery and concurrent critical-care interventions and to determine whether specific patients benefit from acute neurostimulant therapy.

4.9 Strengths and limitations

This review prioritized concurrent comparative evidence, analyzed randomized and observational studies separately, accounted for shared comparators and repeated outcomes, and assessed risk of bias and certainty using established tools. Prespecified sensitivity analyses and cautious interpretation of uncontrolled pre–post changes further reduced the risk of attributing spontaneous recovery to treatment.

The main limitation was the small number of studies and participants contributing to most outcomes, resulting in substantial imprecision, particularly for mortality, long-term functional outcome, and seizures. The limited evidence base also prevented reliable subgroup analyses, meta-regression, and formal assessment of publication bias.

Clinical and methodological heterogeneity remained considerable despite occasionally low statistical heterogeneity. Studies differed in drug, dose, treatment timing, baseline neurological status, sedation, mechanical ventilation, and concurrent neurosurgical or critical-care interventions. Outcome definitions and assessment times also varied, limiting comparability and potentially obscuring treatment-effect heterogeneity.

Moderate and severe TBI could not be analyzed separately because mixed-severity studies generally reported only aggregate outcomes. Classifying entire cohorts according to mean or median baseline GCS would have risked misclassification and ecological bias. The pooled findings therefore apply primarily to severe or predominantly severe TBI, with greater uncertainty for isolated moderate injury.

The GCS was the most frequently reported consciousness measure but may be affected by intubation, sedation, systemic complications, and injuries that limit verbal or motor responses. Paired baseline and follow-up data were often unavailable, preventing pooled change-score analyses. Although reliance on between-group scores at prespecified time points strengthened causal interpretation, it limited assessment of whether treatment altered the trajectory or rate of recovery.

Residual confounding remained important. Sedation and analgesic exposure, ventilatory status, neurosurgical procedures, extracranial trauma, and intracranial lesion characteristics were incompletely and inconsistently reported. Sedative dose and duration were rarely quantified, and the timing of neurological examinations relative to sedation interruption or extubation was often unclear. These variables were seldom available by treatment arm or outcome, precluding adjusted analyses or meta-regression. Consequently, observed GCS differences may partly reflect variations in sedation, airway status, systemic injury, operative treatment, or lesion burden rather than neurostimulant effects.

Finally, adverse-event definitions, ascertainment, and follow-up were inconsistent, limiting comparative safety conclusions. Overall certainty ranged from moderate to very low and was reduced by risk of bias, imprecision, inconsistency, and heterogeneous outcome assessment.

5. Conclusion

Current comparative evidence does not establish that amantadine, methylphenidate, modafinil, zolpidem, or combination regimens improve consciousness or other major clinical outcomes when initiated during acute hospitalization for moderate-to-severe traumatic brain injury. Improvements reported in uncontrolled studies cannot be attributed to treatment because spontaneous recovery and concurrent critical-care interventions remain plausible explanations. Given the low to very low certainty of evidence for most patient-important outcomes, these findings reflect persistent uncertainty rather than definitive ineffectiveness and do not support routine acute use. Adequately powered, agent-specific randomized trials are needed to determine whether selected patients or treatment windows may derive benefit.

Declarations

Author Contributions

- Oscar I. Molina-Romero: conceptualization, methodology, data management, writing – original draft, writing – review and editing.
- Gustavo Adolfo Villegas-Gomez: data management, formal analysis, writing, review, and editing.
- Alejandra Ramirez-Romero: data management, writing, review, and editing.
- Juan Diego Sandoval-Rojas: data management, writing, review, and editing.
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- Edgar Andrés Ordoñez-Bastidas: supervision, review, and editing.
- Jorge A. Carrizosa: supervision, review, and editing.

All authors read and approved the final manuscript.

Prior publication or current submission

All authors confirm that this manuscript, or a substantial part of it, has not been published previously and is not under consideration for publication elsewhere, in whole or in part, in any language, except as an abstract/podium presentation at the XIX International Symposium on Intracranial Pressure and Brain Monitoring (Punta del Este, Uruguay, October 27–30, 2025).

Prior publication or current submission

This is a systematic review and meta-analysis of previously published, de-identified aggregate data; it did not involve new data collection from human participants or animals, and no primary patient-level data were accessed by the authors. Accordingly, this study did not require Institutional Review Board (IRB)/ethics committee approval or informed consent, and none was obtained for the conduct of this review.

The study protocol was prospectively registered in PROSPERO (registration CRD420261325880) prior to data extraction, and conduct followed the PRISMA 2020 guidelines.

Prior publication or current submission

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript. No author received funding, honoraria, consulting fees, or other financial support from any commercial entity related to the subject matter of this review.

Prior publication or current submission

This systematic review and meta-analysis was conducted and reported in accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and checklist. The completed PRISMA 2020 checklist will be uploaded as a supplementary file with this submission (Supplementary Table S2).

Artificial Intelligence Statement

No generative artificial intelligence (AI) or AI-assisted technologies were used in the conception, design, data extraction, statistical analysis, or generation of scientific content, conclusions, or interpretation of this manuscript.

Available data

do not support preferential selection of one agent or combination therapy. Until more reliable comparative evidence is available, acute use should remain cautious, closely monitored, and preferably conducted within prospective registries or clinical trials.

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Tables

Table 1 and 2 are available in the Supplementary Files section.

Figures

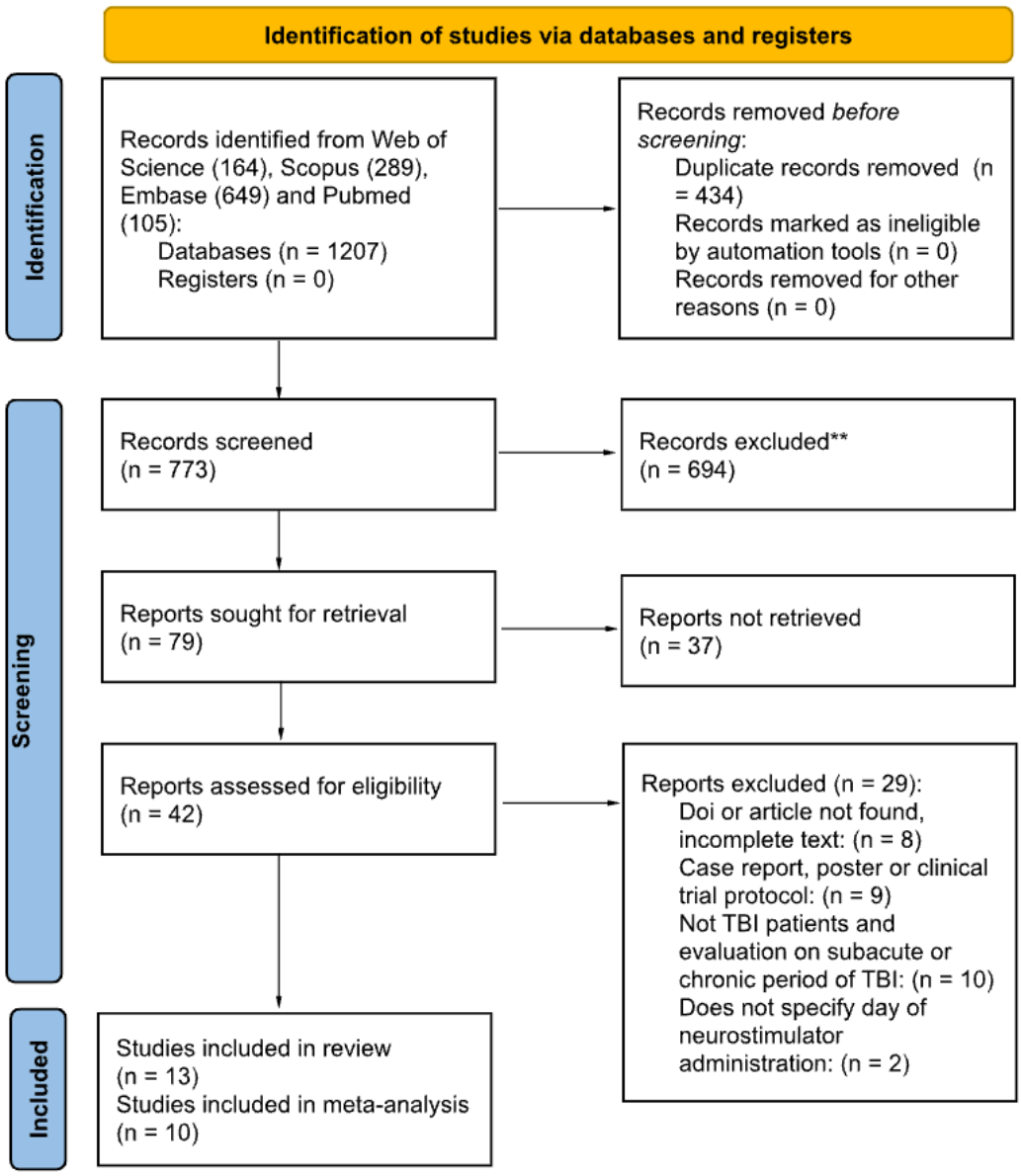


Figure 1

PRISMA 2020 flow diagram for study selection. TBI = Traumatic Brain Injury; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.



Figure 2

Risk of bias assessment. (A) ROBINS-I risk-of-bias traffic-light plot across observational included studies. D1 – bias due to confounding; D2 – bias due to selection of participants; D3 – bias in classification of interventions; D4 – bias due to deviations from intended interventions; D5 – bias due to missing data; D6 – bias in measurement of outcomes; D7 – bias in selection of the reported result. Each circle indicates the risk level for a given domain: green (+) = low risk, yellow (–) = moderate risk, red (!) = critical risk. Most studies showed a low risk of bias, particularly in selection of participants, classification of interventions, deviations from intended interventions, missing data and measurement of outcomes, while moderate and critical risks were mainly related to confounding and selection of the reported result. **(B)** RoB-2.0 risk-of-bias traffic-light plot across randomized included studies. D1 – bias arising from the randomization process; D2 – bias due to deviations from intended interventions; D3 – bias due to missing outcome data; D4 – bias in measurement of the outcome; D5 – bias in selection of the reported result. Each circle indicates the risk level for a given domain: green (+) = low risk, yellow (–) = some concerns, red (×) = high risk. Half of the studies showed a low risk of bias, particularly in deviations from intended interventions and selection of the reported result, while some concerns to high risks were mainly related to the randomization process, missing outcome data and measurement of the outcome.

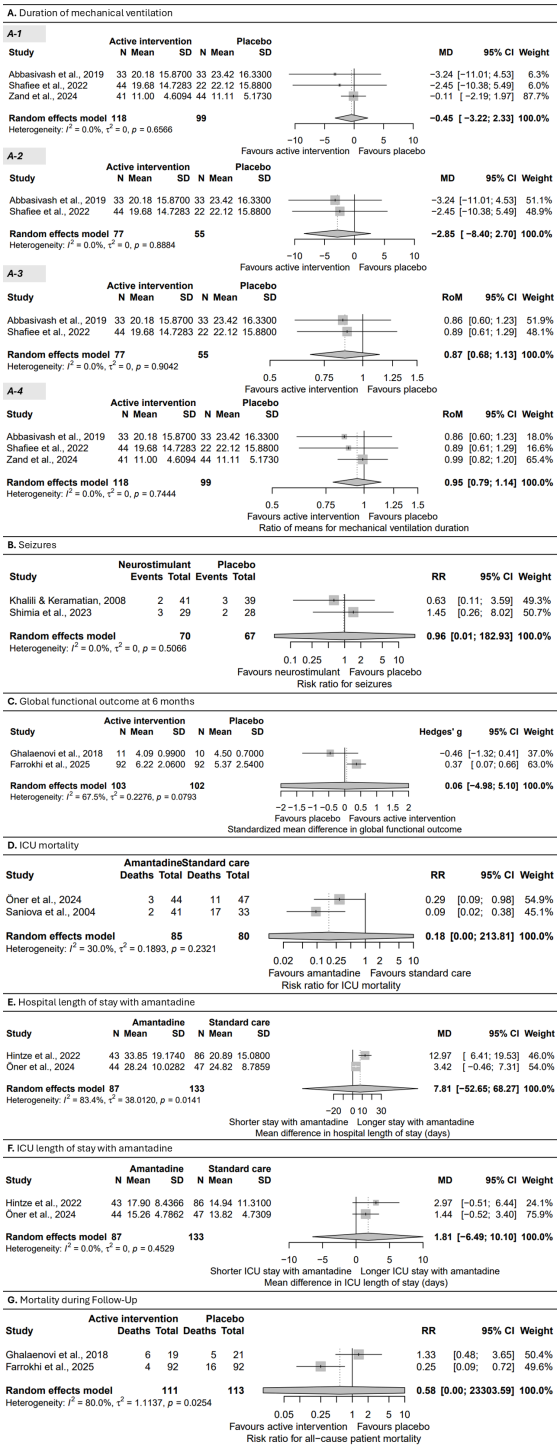


Figure 3

Mechanical ventilation, seizures, functional outcome, mortality, and length of stay after neurostimulant treatment. Forest plots comparing active pharmacological interventions with placebo or standard care for **(A)** duration of mechanical ventilation, expressed as mean difference using the complete ***(A-1)***and restricted ***(A-2)*** datasets and as ratio of means using the restricted ***(A-3)*** and complete ***(A-4)***datasets; **(B)** occurrence of seizures; **(C)** global functional outcome at 6 months; **(D)** intensive care unit mortality

with amantadine versus standard care; **(E)** hospital length of stay with amantadine versus standard care; **(F)** intensive care unit length of stay with amantadine versus standard care; and **(G)** all-cause mortality during follow-up. Pooled estimates were calculated using random-effects models. Squares indicate individual study estimates, with square size proportional to study weight; horizontal lines represent 95% confidence intervals, and diamonds represent pooled estimates. **Abbreviations:** CI, confidence interval; ICU, intensive care unit; MD, mean difference; N, number of participants; RoM, ratio of means; RR, risk ratio; SD, standard deviation; Hedges' *g*, standardized mean difference corrected for small-sample bias; I^2, percentage of total variability attributable to between-study heterogeneity; τ^2, estimated between-study variance.

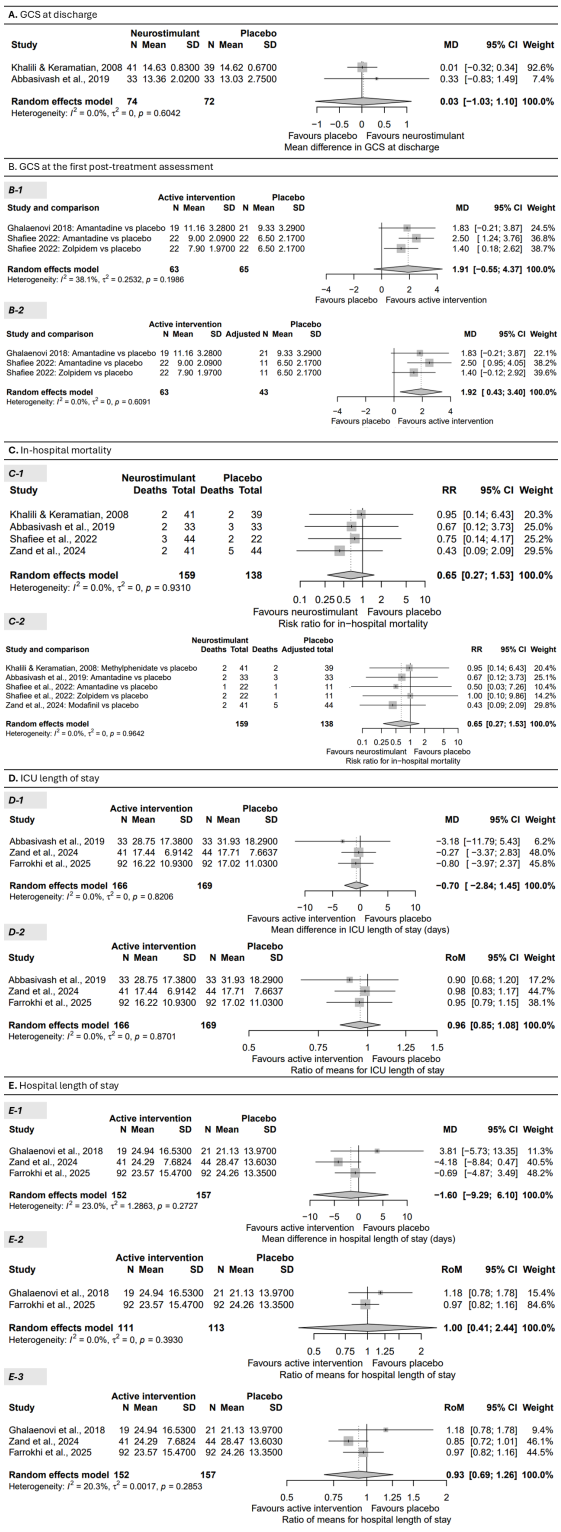


Figure 4

Neurological outcomes, in-hospital mortality, and length of stay after neurostimulant treatment. Forest plots comparing neurostimulant or active pharmacological interventions with placebo for **(A)** Glasgow Coma Scale score at hospital discharge;**(B)** Glasgow Coma Scale score at the first post-treatment assessment, using the original shared placebo group for each comparison ***(B-1)*** and adjustment of the shared placebo group to prevent double counting ***(B-2)***; **(C)** in-hospital mortality, analyzed at the study

level ***(C-1)*** and by individual drug comparison with adjustment of shared placebo participants ***(C-2)***; **(D)** intensive care unit length of stay, expressed as mean difference ***(D-1)*** and ratio of means ***(D-2)***; and **(E)** hospital length of stay, expressed as mean difference using the complete dataset ***(E-1)*** and as ratio of means using the restricted ***(E-2)*** and complete ***(E-3)*** datasets. Pooled estimates were calculated using random-effects models. Squares indicate individual study estimates, with square size proportional to study weight; horizontal lines represent 95% confidence intervals, and diamonds represent pooled estimates.**Abbreviations:** CI, confidence interval; GCS, Glasgow Coma Scale; ICU, intensive care unit; MD, mean difference; N, number of participants; RoM, ratio of means; RR, risk ratio; SD, standard deviation; I^2, percentage of total variability attributable to between-study heterogeneity; τ^2, estimated between-study variance.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.xlsx
- Supplementarymaterial.docx