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REVIEW ARTICLE (META-ANALYSIS)

Participation After Multidisciplinary Rehabilitation for Moderate to Severe Traumatic Brain Injury in Adults: A Systematic Review

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Abstract

Objective: To determine the effectiveness and comparative effectiveness of multidisciplinary rehabilitation programs for moderate to severe traumatic brain injury (TBI) in improving participation-related outcomes in adults. This article presents results of select key questions from a recent Agency for Healthcare Quality and Research comparative effectiveness review.

Data Sources: MEDLINE, Cochrane Central Register of Controlled Trials, and PsycINFO; hand searches of previous relevant reviews.

Study Selection: We included prospective controlled studies that evaluated the effectiveness or comparative effectiveness of multidisciplinary rehabilitation programs delivered to adults with moderate to severe TBI on their participation in life and community.

Data Extraction: We extracted data, assessed risk of bias, and evaluated strength of evidence. Participation was selected as our primary outcome and included measures of productivity (eg, return to employment or military service) and select scales measuring community integration. Only data from studies with a low or moderate risk of bias were synthesized.

Data Synthesis: Twelve studies met our inclusion criteria; of these, 8 were of low or moderate risk of bias (4 randomized controlled trials of 680 patients and 4 cohort studies of 190 patients, sample size 36–366). Heterogeneous populations, interventions, and outcomes precluded pooled analysis. Evidence was insufficient to draw conclusions about effectiveness. Evidence on comparative effectiveness often demonstrated that improvements were not different between groups; however, this evidence was low strength and may have limited generalizability.

Conclusions: Our review used a rigorous systematic review methodology and focused on participation after multidisciplinary rehabilitation programs for impairments from moderate to severe TBI. The available evidence did not demonstrate the superiority of one approach over another. This conclusion is consistent with previous reviews that examined other patient-centered outcomes. While these findings will have little clinical impact, they do point out the limited evidence available to assess effectiveness and comparative effectiveness while highlighting important issues to consider in future comparative effectiveness research on this topic.

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Rehabilitation after traumatic brain injury (TBI) has recently received increased attention from researchers, policymakers, clinicians, payers, advocates, patients, and the media. This attention is for good reason. TBI is widely understood to be a significant public health issue in the United States. Not well understood, however, is how to best rehabilitate individuals with resulting impairments from TBI. In the face of this uncertainty, patients with impairments from TBI and their health care providers must

Study conducted by the Minnesota Evidence-based Practice Center, a collaboration between the Division of Health Policy and Management, University of Minnesota School of Public Health and Center for Chronic Disease Outcomes Research, Minneapolis VA Health Care System, Minneapolis, Minnesota.

Study results presented to Agency for Healthcare Quality and Research, published online June 2012, available at: http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1160&pageaction=displayproduct, and presented as a poster to Academy Health, June 25, 2012, Orlando, FL.

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make treatment decisions with the aim of achieving the best possible outcomes.

TBI incidence demonstrates the significance of the problem. The Centers for Disease Control and Prevention estimated, from hospital records, that 1.7 million TBIs occurred in patients each year from 2002 to 2006. Of these, 1.37 million patients were treated and released from emergency departments, 275,000 were hospitalized, and 50,000 died.[1] Additional TBIs, not reflected in the numbers above, are treated in primary care settings and in military and Department of Veterans Affairs hospitals. The Department of Defense reported more than 4,500 moderate to severe TBIs among all service members in 2010.[2] Major causes of TBIs include falls (35.2%), motor vehicle collisions (17.3%), struck by/against events (16.5%), assaults (10%), other/unknown (21%), and, for military personnel deployed in a combat zone, explosions/blasts.[3]

Moderate to severe TBI more often leads to sustained impairments requiring rehabilitation than mild TBI: 40% of those hospitalized with nonfatal TBI sustain impairments that lead to long-term disability.[4] By one estimate, 2% of the U.S. population lives with TBI-related disabilities,[5] presumably from moderate to severe TBI.

Injury type and level of severity are associated with specific impairments. Penetrating injuries can lead to deficits related to the region of the brain injured, and the more common closed head injuries can result in diffuse brain damage and a range of deficits.[6] Evidence suggests that long-lasting effects of moderate to severe TBI include neurocognitive deficits and impaired social functioning.[7] Psychiatric conditions (ie, depressive and aggressive behaviors, post-traumatic stress disorder, psychoses) are also associated with moderate to severe TBI. Some long-term impairments may not become apparent until well after the injury.[7] Among those hospitalized for TBI, social functioning is adversely affected for at least 1 year and can continue for up to 15 years.[7] These long-term neurocognitive deficits and impaired social functioning make returning to previous roles in the workplace or community especially challenging.

Rehabilitation programs seek to restore an individual's functioning and participation to preinjury levels. During the 1970s and 1980s, research suggested that domain-specific training may be insufficient to rehabilitate patients with frontal lobe damage.[8] Because most TBIs involve the frontal lobe, clinicians began to adopt multidisciplinary approaches to TBI rehabilitation.[8] Multidisciplinary programs are delivered by teams that may include physiatrists, neurologists, neuropsychologists, clinical psychologists, physical and occupational therapists, speech language pathologists, recreation therapists, social workers, nurses, and technicians. Specific programs differ by target patient population, setting, program components, and emphases.

Clinicians and researchers have used a variety of outcomes to assess the effectiveness of rehabilitation. Patient-centered outcomes are those valued by patients.[9] Ultimately, survivors of TBI and their families hope for reintegration into previous roles and activities. Therefore, the goal of TBI rehabilitation is to help patients resume meaningful participation in their homes and social environments, regardless of whether specific impairments can be eliminated.[10] For many brain injury survivors, a final goal of community integration may be return to work (RTW), school, or training, all of which are often classified as "productivity" outcomes. Researchers and practitioners agree that "community integration" outcomes, related to the resumption of societal roles, are important indicators of the effectiveness for TBI rehabilitation.[10] However, these outcomes, while obviously important, have not been utilized extensively in TBI rehabilitation outcomes research.[11]

Although experts have increasingly identified comprehensive multidisciplinary rehabilitation as the best approach for addressing multiple TBI-related impairments, how to best match individual patients to the most appropriate type of program is less clear. This uncertainty results from challenges and limitations inherent in evaluating effectiveness and synthesizing evidence on complex conditions and interventions. Heterogeneity of populations across and within studies makes it difficult to demonstrate effectiveness in original research and compare results across studies in evidence synthesis. Rehabilitation programs can be specific to their setting or may adapt to their populations,[12] resulting in limited generalizability. Not surprisingly, current systematic reviews on this topic arrive at seemingly inconsistent conclusions.

The systematic reviews that have examined brain injury rehabilitation have varied widely with regard to populations, outcomes, and study designs included. For instance, reviews by Cicerone et al[11,13-15] are recognized as demonstrating the effectiveness of cognitive rehabilitation. Cicerone's latest review[15] and a recent Cochrane review of multidisciplinary rehabilitation for acquired brain injury in working-age adults[16] concluded that multidisciplinary programs improved outcomes.[16] However, the recent Institute of Medicine review reported that the evidence on the effectiveness or comparative effectiveness of multimodal cognitive rehabilitation for moderate to severe TBI was not informative.[17] The Institute of Medicine's conclusions drew heavily from randomized controlled trial (RCT) data, included studies predominantly with patients with TBI, and separately assessed effectiveness with the patient-centered outcomes of functional status and quality of life. In contrast, the conclusions from the Cicerone reviews were drawn from a variety of study designs, included a combination of populations with TBI and stroke, assessed effectiveness with patient-centered outcomes as well as intermediate outcomes (ie, neuropsychological test scores), and utilized less rigorous risk of bias and strength of evidence (SOE) assessments. The Cochrane review included controlled trials evaluating rehabilitation for acquired brain injuries in working-age adults. Only 1 recent systematic review[18] focused on participation outcomes after rehabilitation specifically for impairments from TBI. This review included studies of populations with TBI of any severity, addressed interventions relevant to occupational therapy, limited outcomes to community integration, and did not use a rigorous systematic review methodology. They found limited support for certain rehabilitation programs.

Resolving controversy around the effectiveness and comparative effectiveness of TBI rehabilitation is essential. TBI continues to be a major concern for active-duty military, veterans, and civilians. To further explore the evidence on this topic, we conducted a comparative effectiveness review for the Agency for Healthcare Research and Quality (AHRQ) Effective Healthcare

List of abbreviations:

AHRQ	**Agency for Healthcare Research and Quality**
CIQ	**Community Integration Questionnaire**
ICRP	**Intensive Cognitive Rehabilitation Program**
RCT	**randomized controlled trial**
RTW	**return to work**
SOE	**strength of evidence**
TBI	**traumatic brain injury**
TEP	**Technical Expert Panel**

Program (available at http://effectivehealthcare.ahrq.gov/). This article presents a subset of the research questions addressed in the more comprehensive review.[19]

We sought to add to the current body of systematic reviews on this topic by addressing integrated multidisciplinary rehabilitation programs, the most frequently recommended approach for patients with multiple impairments, by specifically focusing on participation outcomes that are valued by patients and their families and have received less attention in previous reviews and by using AHRQ's rigorous comparative effectiveness review process and methodology.

Methods

This topic was nominated by the Medicaid Evidence Based Decisions Project and selected by AHRQ for comparative effectiveness review. The Minnesota Evidence-based Practice Center refined the nominated topic through team meetings and discussions with key informants (individuals knowledgeable about the topic from a variety of perspectives: researchers, clinicians, payers, patients, and caregivers) and drafted a list of key questions to address in the review. These key questions were posted for public comment. We recruited a Technical Expert Panel (TEP) during the public comment period. Our TEP included researchers and clinicians with expertise on TBI rehabilitation. We revised our key questions on the basis of the public comments received. The revised key questions were used to draft a protocol and facilitate discussions with TEP members. The final review protocol reflected feedback from the TEP.

Data sources and searches

We searched MEDLINE, the Cochrane Central Register of Controlled Trials, and PsycINFO through September 2012. We used controlled vocabulary and natural language to describe the condition and interventions, and we used a filter to identify study designs. Appendix 1 shows our search strategy. We also conducted backwards citations searches of recent systematic reviews.

Study selection

Two investigators independently reviewed each citation and full text when deemed necessary to determine eligibility. Disagreements were resolved by consultation between investigators or with a third investigator when necessary. We included English-language RCTs and prospective controlled observational studies of adult patients with moderate to severe TBI treated with a comprehensive multidisciplinary program for sustained cognitive, behavioral, and/or physical impairments. Studies in which fewer than 75% of those enrolled had moderate to severe TBI were excluded. In keeping with the goals of rehabilitation of restoring individuals to roles in their communities, we a priori selected participation measures as primary outcomes. These included productivity and community integration. Many scales that measure community integration in patients with TBI are available. We sought to synthesize evidence using the most valid and reliable scales for this population. We therefore selected scales from those recommended by the Common Data Elements – TBI Outcomes Workgroup.[20] These included the Mayo-Portland Adaptability Inventory,[21] the Craig Handicap Assessment and Reporting Technique,[22] and the Craig Handicap Assessment and Reporting Technique Short Form.[23] We also included the Community Integration Questionnaire (CIQ),[24] which was commonly used in earlier research.

Data extraction, strength of evidence, and quality assessment

Trained and experienced extractors extracted study and patient characteristics and results for selected outcomes. One investigator extracted the relevant data, and a second investigator reviewed the extracted data for accuracy.

We developed 2 instruments to assess the risk of bias for each individual study, 1 for RCTs and 1 for observational studies. Our instruments were developed using the Cochrane Risk of Bias Tool[25] and the Research Triangle Institute Observational Studies Risk of Bias and Precision Item Bank.[26] For RCTs, we modified the Cochrane Risk of Bias tool[25] to address specific items that could lead to the risk of bias on this topic. Because of the complex nature of the interventions, we incorporated items from the Research Triangle Institute Observational Studies Risk of Bias and Precision Item Bank[26] to evaluate intervention and comparison definitions, implementation, and outcomes issues (consistent measurement, validity and reliability of scales, objective vs subjective measures, providers vs self-report). Building on the work of other researchers,[27] we assessed whether the intervention definitions provided adequate detail, including identification of the theory or model driving the specific studied intervention, thorough details about intervention components, and documentation of the intervention in manuals or other publications. We also reviewed studies for validation that the interventions were effectively implemented via staff training and/or fidelity checks. Because many outcomes were measured using scales that can increase the risk of bias especially when they are subjective and/or self-report, we added an item assessing the quality and validity of the scale to our risk of bias assessment forms. We also modified the Cochrane questions to simplify the evaluation of each component by directly answering questions instead of assessing the risk of bias posed for each individual element. Because blinding of participants and personnel is generally not feasible in research on complex interventions, we did not include this element in our assessment of the risk of bias. The resulting items on our RCT risk of bias instrument included randomization method, allocation concealment, blinding of outcome assessment, intervention and control description, intervention implementation, outcome measurement, incomplete outcome data, selective outcome reporting, and other issues (as identified by the investigator). Our risk of bias assessment instrument for observational studies included relevant items that were consistent with items on the RCT instrument, and additional items relevant to selection bias and statistical analysis. While funding source can influence the potential risk of bias in individual studies, we felt the risk to be low for this topic and did not include elements specifically assessing the risk of bias created by the study funding source. The last item on each risk of bias assessment instrument assigned an overall risk of bias to the study. Two investigators assessed the risk of bias for each study and assigned summary scores of low, moderate, or high on the basis of their judgment about the collective risk of bias. Consensus on the overall risk of bias was achieved for all studies except one. A third investigator was consulted to reconcile this risk of bias assessment, and the consultation resulted in a moderate versus high risk of bias assessment. Studies with an overall high risk of bias were not used in data synthesis.

We evaluated the overall SOE for each primary outcome or comparison using methods developed by AHRQ.[28] SOE was evaluated on 4 domains:

1. Risk of bias (do the studies for a given outcome or comparison have good internal validity?). The risk of bias, based on study design and conduct, was rated low, moderate, or high.
2. Consistency (the degree of similarity in effect sizes—ie, same direction of effect across studies). Consistency is rated consistent or inconsistent if possible. When evidence on comparisons was based on a single study, we recorded "single study" for this domain and did not downgrade the SOE.
3. Directness (reflecting a single, direct link between the intervention of interest and the outcome). Directness can be either direct or indirect. Because we assessed the SOE only for primary outcomes, we considered all included evidence to be direct.
4. Precision (degree of certainty surrounding an effect estimate of a given outcome). Precision is either precise or imprecise. A precise estimate is one that would yield a clinically meaningful conclusion. Relative risk estimates for dichotomous outcomes were determined imprecise if the relative risk increases or reductions exceeded 25%; continuous outcomes were considered imprecise if the upper or lower confidence interval crossed an effect size of 0.5 in either direction.[29]

Two investigators worked independently to qualitatively rate each component and the overall SOE. Consensus was achieved on overall SOE assessments; disagreements in a few individual domain evaluations were reconciled through discussion among project team members. We rated the overall evidence for each outcome and comparison as follows[28]:

1. High: High confidence that the evidence reflects the true effect; further research is very unlikely to change the confidence in the estimate of effect.
2. Moderate: Moderate confidence that the evidence reflects the true effect; further research may change our confidence in the estimate of effect and may change the estimate.
3. Low: Low confidence that the evidence reflects the true effect; further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
4. Insufficient: Evidence either is unavailable or does not permit a conclusion.

Data synthesis

The heterogeneity of study settings, populations, interventions, controls, and outcomes precluded quantitative synthesis of results. In these cases, a narrative or qualitative approach to data synthesis is appropriate. In our qualitative syntheses, we grouped studies by population and intervention setting to see whether we could identify meaningful patterns. For instance, we attempted to group interventions by rehabilitation program types described in the literature[30,31] to determine whether specific types of programs were more effective than others. However, the limited number of studies and heterogeneity in populations, settings, and interventions combined with null results in several studies did not highlight meaningful patterns. To assess generalizability, we evaluated whether included characteristics of population or injury differed from those described by population studies of TBI, and whether included programs were those typically used or accessible in current practice.[32]

Role of the funding source

AHRQ supported the completion of this review and provided copyright release for this article, but had no role in the literature search, data analysis, conduct of the study, preparation of the review, or interpretation of the results. Therefore, the risk of bias in this review created by the funding source is low. In addition, team members and TEP members were required to submit signed disclosures regarding related financial or professional affiliations. Affiliations of TEP members did not exclude members from participation; however, their comments were interpreted by investigators with reported affiliations in mind. In addition, review protocol is made publicly available and AHRQ reports undergo extensive public and peer review. Review comments and responses are made publicly available as well.

Results

Results of literature searches

Our bibliographic database searches identified 1761 unique references (fig 1). Review of titles and abstracts identified 174, and hand searching identified 12 references meriting full-text review, based on which 12 unique studies met inclusion criteria. The most common reason for exclusion was the lack of a comparison group; 62 studies were excluded on this basis. Other common reasons for exclusion included no intervention, lack of participation or community reintegration outcome, ineligible study design (eg, retrospective or uncontrolled observational studies), and populations with fewer than 75% with moderate to severe TBI.

Study characteristics

Four of the 12 eligible studies were judged to have a high risk of bias, and thus excluded from analysis,[33-36] leaving 8 studies (4 RCTs and 4 cohort studies) used to assess SOE. Of these 8 studies, 1 was rated low risk of bias and 7 were rated moderate risk of bias.

Sample sizes ranged from 36 to 366. Six studies were conducted in the United States and 2 in other countries (United Kingdom and Finland). Subjects were predominantly men (85%) and young relative to the adult population of the United States (mean age, 31y). Other demographic statistics were less often reported. Median time since injury varied widely between studies, from 1 to 45 months with a median of 19 months. Two studies specifically restricted enrollees to those within 3[37] or 6[38] months of injury. The rehabilitation programs studied varied in length and intensity. The majority of studies were observational or pragmatic RCTs; therefore, studied programs likely reflect rehabilitation programs offered in these settings. Appendix 2 provides a summary of included studies (table A2-1), outcomes tables (tables A2-2 and A2-3), and an evidence table (table A2-4). Study results and the overall SOE for each comparison and primary outcome appear in table 1.

Effectiveness

Productivity

One of the observational studies compared a neuropsychological rehabilitation program to a no-treatment group.[39] This small cohort study (n=32) found no significant differences in RTW

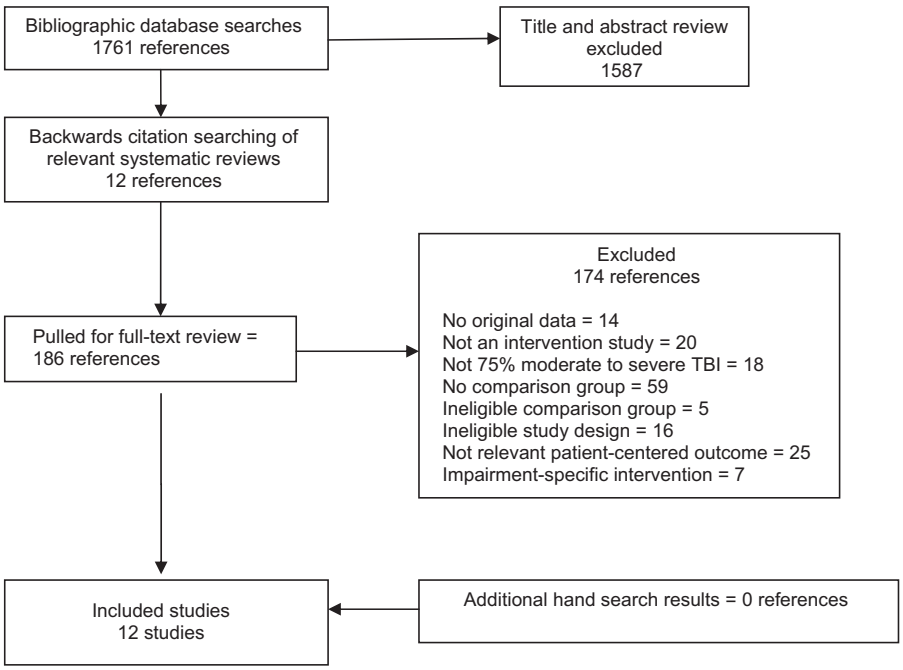

Fig 1 Literature flow diagram for multidisciplinary rehabilitation for moderate to severe TBI in adults.

between groups at 6 to 24 months posttreatment. However, this evidence was judged to be insufficient due to concerns about the risk of bias and lack of precision.

Comparative effectiveness

Productivity

Six studies addressed the comparative effectiveness of different rehabilitation programs with respect to productivity outcomes.[37,38,40-43] Two larger RCTs found no productivity differences between groups of military personnel and veterans receiving different treatments soon after injury.[37,38] Salazar et al[37] compared a limited home treatment program with inpatient rehabilitation and found equivalent rates of RTW and fitness for duty at 1 year among military personnel who started treatment within 3 months of injury and who had Rancho Los Amigos cognitive levels of 7. Vanderploeg et al[38] also found equivalent rates of RTW at 1 year among veterans or active-duty military personnel within 6 months of injury enrolled in a functional experiential versus cognitive didactic rehabilitation program. In both trials, uncontrolled and unmeasured factors between the end of the rehabilitation program and 1-year follow-up could have influenced results. A third RCT found that a 4-month Intensive Cognitive Rehabilitation Program (ICRP) compared to standard treatment resulted in a moderate end-of-treatment increase in productivity for chronically impaired civilian survivors of moderate to severe TBI. Productivity rose from 9% to 47% among ICRP participants and from 12% to 21% among those in standard care.[40] This difference disappeared at the 6-month posttreatment follow-up, by which time productivity among participants in the standard program had improved to 50%, a level no longer significantly different from that found with ICRP, which was 60%. The authors reported that participants in the standard group received more rehabilitation during the follow-up period than participants of the ICRP group, which may have contributed to the increase in productivity. This evidence was low strength because it was derived from 1 moderately sized RCT with a moderate risk of bias. The remaining 3 studies provided insufficient evidence to draw conclusions about comparative effectiveness because they were relatively small cohort studies with a moderate risk of bias.

Community integration

One RCT and 1 cohort study examined group differences in CIQ scores.[40,44] However, neither found significant group differences in CIQ scores posttreatment (ICRP = 12.9, standard rehabilitation = 11.7 in RCT[40]; ICRP = 16.8, standard rehabilitation = 16.1, unadjusted in cohort study[44]). However, a greater proportion of ICRP participants achieved clinically meaningful improvements compared with those in the standard rehabilitation group in the cohort study.[44] Clinically significant improvement (4.2 CIQ points) was seen in 52% of the ICRP group compared with only 31% of the standard rehabilitation group, indicating that ICRP participants were 2.5 times more likely than standard program participants to achieve a clinically significant improvement in CIQ score. However, the authors note that the ICRP participants were farther from injury and had significantly lower levels of community integration before treatment, which may have had an impact on results. The RCT did not assess trends in clinically meaningful change, and results of the cohort study were not adjusted for confounding. We therefore concluded that the ICRP and the standard rehabilitation were not different with respect to posttreatment CIQ scores. This evidence was low strength because it was derived primarily from 1 moderately sized RCT with a moderate risk of bias.

Harms

In the single study that reported on harms, no adverse effects related to treatment were observed.[38]

Table 1 Summary and SOE of effectiveness and comparative effectiveness of multidisciplinary postacute rehabilitation for TBI

Population	Intervention/Comparator	Outcome	Conclusion	SOE (Primary Domains Impacting the SOE)
Active-duty military personnel with moderate to severe closed head injury treated within 3mo of injury[37]	Inpatient hospital rehabilitation program (8wk) vs limited home treatment	Return to gainful employment at 1y posttreatment	No difference between groups	Low (moderate risk of bias, single study)
		Fitness for military duty at 1y posttreatment	No difference between groups	Low (moderate risk of bias, imprecise, single study)
Veterans or active-duty military personnel with moderate to severe closed head injury treated within 6mo of injury[38]	Functional-experiential vs cognitive-didactic rehabilitation programs for varying durations	Return to gainful employment at 1y posttreatment	No difference between groups	Low (moderate/low risk of bias, imprecise, single study)
Chronically impaired patients with primarily moderate to severe TBI[40,44]	Intensive cognitive rehabilitation (16wk) vs standard rehabilitation (16wk)	Community-based employment at the end of treatment	Statistically higher proportion intensive cognitive rehabilitation group employed	Low (moderate risk of bias, single study)
		Community-based employment at 6mo posttreatment	No difference between groups	Low (moderate risk of bias, single study)
		CIQ at the end of treatment	No difference between groups	Low (medium risk of bias, imprecise, consistent)
		CIQ at 6mo posttreatment	No difference between groups	Low (medium risk of bias, single study)

NOTE. This table presents a summary of the findings for this systematic review and the overall SOE for each comparison and outcome.

Discussion

Our review found the currently available evidence too limited to draw robust conclusions about the effectiveness and comparative effectiveness of multidisciplinary rehabilitation programs for moderate to severe TBI in adults with respect to participation outcomes. Specifically, we found insufficient evidence to assess effectiveness, and identified few well-designed studies with which to address comparative effectiveness. Our results are consistent with the Institute of Medicine review evaluating evidence on integrated programs with respect to other patient-centered outcomes.[17] Neither review suggests that rehabilitation is ineffective, and both recommend future research to enhance understanding about which types of rehabilitation interventions best serve which populations.

The comparative effectiveness studies we reviewed typically demonstrated improvements in patient-centered outcomes in all treated groups. However, the available evidence showed no robust benefit of one rehabilitation approach over another. Low-strength evidence indicated that ICRP may lead to earlier productivity than standard rehabilitation for patients needing intensive rehabilitation at least 3 months postinjury. We describe this finding as earlier participation because low-strength evidence also indicated that productivity rates did not differ significantly between groups at 6 months posttreatment. Although the ICRP program did not result in better CIQ scores posttreatment than standard rehabilitation, Cicerone et al[44] did find greater proportions of ICRP participants making clinically meaningful improvements in community integration when compared with those in standard rehabilitation. This suggests that the effectiveness of ICRP relative to standard rehabilitation merits further investigation.

Although the literature we examined demonstrated no clear superiority of one type of program over another, these results could be an embodiment of the context in which the studies were conducted. For instance, Salazar et al[37] enrolled patients whose functional status and social support were sufficient to allow for randomization to home care. Thus, the fact that this group experienced similar improvements to those randomized to inpatient rehabilitation may be specific to their relatively low levels of impairment. Validating this possibility, these authors' post hoc subgroup analysis of those with more serious injuries found greater improvements from inpatient rehabilitation. A similar situation occurred in the Vanderploeg et al[38] study, in which certain patient subgroups fared better with one rehabilitation approach versus the other as detected in post hoc analysis.

Ultimately, while compared programs often achieved similar outcomes, post hoc analyses hinted that different patient subgroups responded better to certain types of treatments. We cannot draw conclusions from these subgroup analyses; however, they may suggest that patients might best be rehabilitated when matched to a specific program most likely to benefit them. Higher quality evidence testing subgroups identified a priori examining these relations could provide clinically meaningful information.

Future research to identify and test hypothesized interactions between patient types and rehabilitation program approaches

would provide this evidence. These studies would require large sample sizes and an appropriate level of funding to be feasible. To create interpretable results, the researchers would need to plan subgroup analyses a priori and adequately power their studies for these subgroup analyses. Prospective controlled observational studies would likely encounter fewer ethical and feasibility issues, but would need to appropriately address selection bias.

Study limitations

Conducting and synthesizing research on this topic is impeded by the complexity of the impairments associated with moderate to severe TBI and multidisciplinary rehabilitation programs, as well as by the significant number of variables and interactions among variables that affect recovery and rehabilitation outcomes (comorbidities, social support, impairment levels, how and when outcomes are assessed, etc). These factors make it difficult to conduct RCTs and for synthesized evidence to earn high SOE assessments.

Generalizability of these results may be limited. The studies evaluated for this review may be applicable to the specific populations targeted by the examined interventions (eg, military populations, those with significant disabilities, without other psychiatric diagnoses, and chronically impaired). In addition, many of the interventions and control conditions seemed to be embodiments of their local rehabilitation systems, further limiting generalizability and making replicability in other contexts challenging.

Most studies excluded individuals with substance abuse or psychiatric diagnoses, both of which are common in the TBI population.[45] Inconsistent insurance coverage for rehabilitation services[6] also presents implications regarding generalizability and relevance. This is especially salient because TBI disproportionately affects certain population groups known to have lower rates of health insurance, including men, those aged 15 to 24 years, and those with lower socioeconomic status, which influences the accessibility of these programs.[7] Therefore, available evidence may not be relevant to the many individuals unable to access comprehensive rehabilitation programs.

Despite many attempts to synthesize the evidence relevant to the effectiveness and comparative effectiveness of multidisciplinary rehabilitation programs for moderate to severe TBI in adults, research gaps remain. Additional comparative effectiveness reviews cannot satisfy these gaps until additional high-quality research is completed. A detailed AHRQ report on the future research needs regarding this topic is forthcoming. The highest priority may be conceptual work designed specifically to overcome the shortcomings of current research and therefore help ensure that future comparative effectiveness studies add value and advance the field by answering pressing questions.

Methodologic considerations for future comparative effectiveness studies include designing studies with adequate power to detect differences in groups, appropriate control for confounding, consistent and appropriate outcomes measurement instruments selected a priori, blinding of outcomes assessors, adjustment for multiple comparisons, consistent fidelity checks and documentation and training in intervention protocols, and identification and exploration of the use of minimum clinically important differences. Studies designed with subgroup analysis planned a priori would help to answer more specific questions relating specific program types to specific patient or impairment types as suggested by previous post hoc analysis. Effectiveness research, for which a no-treatment control group is needed, is unlikely to be conducted because of ethical concerns. However, comparative effectiveness studies may be more feasible (and waitlist controls more acceptable) in studying chronic impairments. Research currently underway utilizing the practice-based evidence approach[46] could provide valuable insight regarding when and how these complex interventions work by enabling large samples and the collection of a large number and variety of variables.

Conclusions

Ultimately, the available evidence provided little clinically meaningful information about the overall effectiveness or comparative effectiveness of multidisciplinary rehabilitation programs for adults with impairments from moderate to severe TBI with respect to participation outcomes. Evidence on effectiveness was insufficient to draw conclusions. Evidence on comparative effectiveness typically demonstrated improvements in participation outcomes in both the intervention rehabilitation program and the comparison rehabilitation program without clear superiority of one program over another. However, the low strength of this evidence and results from specific post hoc analyses within these studies prevent us from concluding that compared rehabilitation programs achieve similar improvements in participation outcomes. This review speaks to the critical need for resources and clinical and scientific commitment—to support both establishing criteria for and conducting high-quality research on this topic.

Keywords

Brain hemorrhage, traumatic; Brain injuries; Brain injuries, chronic; Diffuse axonal injury; Rehabilitation

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Appendix 1 Literature Search Strings

Ovid MEDLINE search strategy

1 Epidemiologic studies/
2 exp case control studies/
3 exp cohort studies/
4 Case control.tw.
5 (cohort adj (study or studies)).tw.
6 Cohort analy$.tw.
7 (Follow up adj (study or studies)).tw.
8 (observational adj (study or studies)).tw.
9 Longitudinal.tw.
10 randomized controlled trial/
11 clinical trial/
12 clinical trial, phase i.pt.
13 clinical trial, phase ii.pt.
14 clinical trial, phase iii.pt.
15 clinical trial, phase iv.pt.

Appendix 1 (continued)

16 controlled clinical trial.pt.
17 randomized controlled trial.pt.
18 multicenter study.pt.
19 clinical trial.pt.
20 or/1-19
21 Craniocerebral Trauma/
22 exp Brain Injuries/
23 Cerebrovascular Trauma/
24 brain injur*.ti,ab.
25 head injur*.ti,ab.
26 tbi.ti,ab.
27 or/21-26
28 20 and 27
29 Rehabilitation/
30 rehab*.ti,ab.
31 neurorehabilitation.ti,ab.
32 29 or 30 or 31
33 28 and 32
34 limit 33 to "all child (0 to 18 years)"
35 limit 34 to "all adult (19 plus years)"
36 33 not 34
37 35 or 36
38 limit 37 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or congresses or dictionary or directory or in vitro or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or patient education handout or periodical index or portraits or video-audio media or webcasts)
39 37 not 38
40 limit 39 to yr = "1980 -Current"

PsycINFO search strategy

1 epidemiologic studies.mp.
2 case control.mp.
3 exp Longitudinal Studies/
4 (cohort adj (study or studies)).tw.
5 Cohort analy$.tw.
6 (Follow up adj (study or studies)).tw.
7 (observational adj (study or studies)).tw.
8 longitudinal.mp.
9 randomized controlled trial.mp.
10 clinical trial.mp. or exp Clinical Trials/
11 controlled clinical trial.mp.
12 phase i clinical trial.mp.
13 phase ii clinical trial.mp.
14 phase iii clinical trial.mp.
15 phase iv clinical trial.mp.
16 multicenter study.mp.
17 or/1−16
18 exp Traumatic Brain Injury/or exp Head Injuries/or craniocerebral trauma.mp.
19 brain injur*.mp.
20 exp Cerebrovascular Accidents/ or cerebrovascular trauma.mp.
21 head injur*.mp.
22 tbi.mp.
23 or/18−22
24 17 and 23
25 exp Rehabilitation/or exp Neuropsychological Rehabilitation/ or rehabilitation.mp.
26 rehab*.mp.
27 exp Neurorehabilitation/or neurorehabilitation.mp.
28 or/25−27
29 24 and 28
30 limit 29 to (100 childhood <birth to age 12yrs> or 120 neonatal <birth to age 1mo> or 140 infancy <age 2 to 23mo> or 160 preschool age <age 2 to 5yrs> or 180 school age <age 6 to 12yrs> or 200 adolescence <age 13 to 17yrs>)
31 limit 30 to ("300 adulthood <age 18yrs and older>" or 320 young adulthood <age 18 to 29yrs> or 340 thirties <age 30 to 39yrs> or 360 middle age <age 40 to 64yrs> or "380 aged <age 65yrs and older>" or "390 very old <age 85yrs and older>")
32 29 not 30
33 31 or 32
34 limit 33 to yr = "1980 -Current"

Cochrane central register of controlled trials search strategy

1 traumatic brain injur* and rehab*

PEDro search strategy

1 traumatic brain injur* AND rehab*

Appendix 2 Summary of Study Characteristics and Outcomes

Table A2-1 Summary of study population characteristics

Characteristic	Mean (Range) Unless Otherwise Noted	Number of Trials Reporting
Total number of patients evaluated	870 (36—366)	8
Randomized trials, number of patients	680 (49—366)	4*†‡§
Nonrandomized studies, number of patients	190 (36—59)	4§||¶#
Age of subjects (y)	31 (25—38)	8
Sex, male, % of patients	85 (68—94)	8
White race/ethnicity, % of patients	70 (69—75)	3*†‡
Married, % of patients	28 (25—35)	3*†‡
Education (y)	13 (12—13)	4*¶#
Education, high school or greater, % of patients	94	1†
Education, some college or greater, % of patients	42	1‡
Employment status, preinjury	91 (81—100)	7*†‡§||¶#
TBI severity, % mild (studies that included patients with minor TBI)	12 (11—13)	2*¶††
Time postinjury (mo)	12 (1.3—45)	7*†‡||¶#
Time postinjury (mo), median	19 (1.3—45)	7
TBI etiology-motor vehicle collision, % of patients	63 (38—67)	4†‡§||
TBI etiology-assault, % of patients	11 (5—19)	4†‡§||
TBI etiology-fall, % of patients	15	2†§‡‡
History of psychiatric illness/treatment, % of patients	19 (13—22)	2*‡
History of alcohol and/or substance abuse, % of patients	31 (21—37)	2*‡
Studies done in the United States, number of patients	705 (36—366)	7*†‡¶#g
Studies done outside the United States, number of patients	165	2§||§§

* Cicerone et al.[40]
† Vanderploeg et al.[38]
‡ Salazar et al.[37]
§ Rattok (1992)[42]
|| Sarajuuri et al.[43]
¶ Cicerone (2004).[44]
# Prigatano et al.[39]
†† The remaining 4 studies included participants with only moderate to severe TBI.
‡‡ Sarajuuri et al[43] combined fall and blunt object injury (33% of TBI).
§§ Finland and United Kingdom.

Appendix 2 (continued)

Table A2-2 Productivity outcomes

Study Design, Outcome, and Description	Treatment Arms	% Working or Productive (n/N) Before Treatment	% Working or Productive (n/N) After Completion of Treatment	Treatment vs Control at Endpoint
Cicerone et al[40]	Intensive cognitive rehabilitation	9	47	RR: 2.29
RCT		(3/34)	(16/34)	(1.08–4.84)
Productive*		12	21	$P=.03$
posttreatment (16wk)	Standard neurorehabilitation	(4/34)	(7/34)	
Vanderploeg et al[38]			35	RR: 0.91
RCT	Functional-experiential	NR	(58/164)	(0.69–1.20)
RTW† at 1y postprotocol			39	$P=.50$
treatment	Cognitive-didactic	NR	(65/167)	
Salazar et al[37]			90	RR: 0.95
RCT	Hospital	NR	(60/67)	(0.85–1.05)
RTW‡ in 12mo posttreatment			94	$P=.33$
	Home	NR	(50/53)	
Salazar et al[37]			73	RR: 1.11
RCT	Hospital	NR	(49/67)	(0.87–1.41)
Fitness for duty in 12mo			66	$P=.41$
posttreatment	Home	NR	(35/53)	
Greenwood et al[41]			24	RR: 0.84
RCT (hospitals — not patients)	Case management	100 (42/42)	(10/42)	(0.42–1.68)
At competitive work			28	$P=.62$
6mo postinjury	Conventional rehabilitation	96 (54/56)	(15/53)	
Sarajuuri et al[43]		5	89	RR: 1.63
Prospective cohort	Comprehensive neurorehabilitation	(1/19)	(17/19)	(1.06–2.49)
Productive§ 2y			55	$P=.02$
posttreatment	Conventional rehabilitation	NR	(11/20)	
Rattok et al[42]	Treatment mix 1 (balanced package, including cognitive remediation and small group interpersonal communication training)	NR¶	70 (16/23)	$P=.33$ between all groups
Prospective cohort				
Productive‖ 9mo posttreatment				
	Treatment mix 2 (similar to mix 1 stressing small group interpersonal communication training but without cognitive remediation)	NR¶	89 (16/18)	Treatment mix was unrelated to the number of patients attaining employment
	Treatment mix 3 (emphasis on individualized cognitive remediation but without small group interpersonal communication training)	NR¶	78 (14/18)	
Prigatano et al[39]	Neuropsychological rehabilitation		50	
Prospective cohort		NR	(9/18)	$P=.49$
RTW# at follow-up			36	
(treatment was 6mo)	Controls	NR	(5/14)**	

NOTE. RRs for dichotomous outcomes and effect sizes for continuous outcomes were calculated in Review Manager 5.1 (Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2011).
Abbreviations: NR, not reported; RR, risk ratio (95% confidence intervals).

* According to Vocational Integration Scale dichotomized into productive (supported, transitional, or competitive) vs nonproductive (unemployed or sheltered employment).

† Current status of paid employment or school enrollment, either full-time or part-time, not sheltered workshop.

‡ Work defined working either full-time (≥35h/wk) or part-time (≤35h/wk) in gainful military or civilian employment.

§ Defined as working, studying, or participating in volunteer activities.

‖ Productive employment.

¶ All subjects in the study had "unsuccessful vocational rehabilitation" prior to study entry.

Defined as gainfully employed or actively engaged in a realistic school program at time of follow-up.

** Seventeen controls total, but 3 were excluded (lost to follow-up).

Appendix 2 (continued)

Table A2-3 Community Integration Questionnaire

Study Design, Outcome, Measurement	Treatment Arms	Score ± SD		ES (95% CI) for Treatment vs Control; Comments
		Before Treatment	After Completion of Treatment	
Cicerone et al[40] RCT Self-report under supervision	ICRP (n=34)	11.2±3.4	12.9±3.4 $P<.05$ vs before treatment	ES=0.30 (−0.18 to 0.78) No significant differences between groups but intensive cognitive rehabilitation participants showed greater improvements on the CIQ
	Standard neurorehabilitation program (STD) (n=34)	12.1±4.0	11.7±4.4	
Cicerone[44] Prospective cohort Administered and scored according to original procedures (Willer et al[35])	ICRP (n=27)	11.6±4.6	16.8±4.2 ES vs before treatment 1.16 (0.59−1.74)	ES=0.14 (−0.38 to 0.67) 52% of the ICRP participants showed clinically significant improvement compared with 31% of the SRP participants (OR=2.41 [0.8−7.2])
	Standard neurorehabilitation (SRP) (n=29)	13.7±4.4	16.1±5.4 ES vs before treatment 0.48 (−0.04 to 1.00)	The ICRP group exhibited over twice the magnitude of treatment effect on total CIQ than the participants receiving SRP (1.20 vs 0.49)

NOTE. Risk ratios for dichotomous outcomes and for continuous outcomes were calculated in Review Manager 5.1 (Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2011).
Abbreviations: ES, effect size; OR, odds ratio; CI, confidence interval.

Appendix 2 (continued)

Table A2-4 Characteristics of included studies

Study Description	Inclusion/Exclusion Criteria	Demographic/Preinjury Characteristics	TBI Characteristics	Postinjury Characteristics
Cicerone[44] Study design Prospective cohort Sample size 57 Location Edison, NJ Setting Community-based, postacute outpatient brain injury rehabilitation program Interventions • ICRP group (n=27) • (Control) Standard neurorehabilitation program (SRP) (n=29) Primary outcomes CIQ	Inclusion criteria • Medically stable • Independent in basic self-care skills • Cognitive ability to participate in treatment • Medical documentation TBI • 18y or older • Adequate language expression and comprehension Exclusion criteria • Current substance use or psychiatric disturbance precluding effective treatment • No available family member or person to participate in program	Age (y), mean ± SD • ICRP 38±10.6 • SRP 37±12.0 Sex (% male) • ICRP 63 • SRP 79 Race/ethnicity NR Education (y), mean ± SD • ICRP 13.2±1.7 • SRP 13.0±2.2 Employment status (% competitively employed) • ICRP 96 • SRP 97 Income NR Marital status NR Military/veteran NR Insurance status NR Prior TBI NR Preexisting psychiatric conditions NR	Severity (% moderate/severe) • ICRP 89 • SRP 90 Severity definition NR Time since injury (mo), mean ± SD • ICRP 33.9±4.8 • SRP 4.8±9.5 TBI etiology NR Area of brain injured NR Other injury characteristics NR	Comorbidities Psychiatric comorbidities not described, although subjects identified with current substance use or psychiatric disturbance that would preclude effective treatment for their cognitive deficits were not admitted. Psychiatric subjects were guided to the intensive cognitive group. Compensation seeking NR Acute rehabilitation history NR Concomitant treatment NR
Cicerone et al[40] Study design RCT Sample size 68 Location Edison, NJ	Inclusion criteria • Medical documentation of TBI based on primary source within 24h of injury • At least 3mo postinjury • 18–62y of age • Adequate language expression and comprehension (English) • Judged to require at least 4mo comprehensive treatment	Age (y), mean ± SD ICRP: 39±11 STD: 35±12.4 Sex (% male) 68 Race/ethnicity 75% white, 10% black, 12% Hispanic, 3% Asian	Severity (%) Mild: 13 Moderate: 24 Severe: 59 Severity definition Any combination of initial GCS score, duration of unconsciousness,	Comorbidities NR Compensation seeking status NR Acute rehabilitation history (% inpatient rehabilitation) ICRP: 77 STD: 85

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Appendix 2 (continued)

Table A2-4 (*continued*)

Study Description	Inclusion/Exclusion Criteria	Demographic/Preinjury Characteristics	TBI Characteristics	Postinjury Characteristics
Setting Postacute brain injury rehabilitation center in suburban hospital Interventions • ICRP • Standard neurorehabilitation (STD) Primary outcomes • CIQ • Vocational Integration Scale (community-based employment) Secondary outcomes • Perceived Quality-of-Life (PQOL) scale	• Clinically appropriate for either arm of treatment • Capable of attending treatment 3d/wk • Capable of giving informed consent Exclusion criteria • Active psychiatric illness, substance abuse, or pain that may prevent compliance with treatment	Education (HS or <, some college, college graduate) Employment status 79% employed, 4% unemployed, 2% homemakers, 13% students, 2% retired Income NR Marital status (% married) 35 Military/veteran status NR Insurance status NR Prior TBI 4% Preexisting psychiatric conditions (%) Psychiatric illness 13 Substance abuse 21	duration of PTA, and positive neuroimaging available from primary medical records Time since injury (mo), mean ± SD ICRP = 49.6±76.5 STD = 37.0±58.2 TBI etiology NR Brain area injured NR Other injury characteristics NR	Concomitant treatment NR
Greenwood et al[41] Study design Prospective controlled unmatched nonrandomized study Sample size 126 (outcomes for 118) Location 4 district general hospitals and 2 university teaching hospitals with neurosurgical units Setting London and environs Interventions • Case managed (CM) (n = 56) • Control (n = 70)	Inclusion criteria • Closed head injury • Aged 16–60y • Been in coma for 6h or had a PTA >48h • Caregiver was resident in district • Informed consent Exclusion criteria • Received hospital treatment for drug or alcohol misuse • Aged 16–60y • Psychiatric disturbance, or a disorder of the central nervous system during the previous year • No fixed abode or if follow-up unlikely	Age (y), mean ± SD • CM 31.6±14.4 • Control 30.7±14.0 Sex (% male) • CM 69.6 • Control 75.7 Race/ethnicity NR Education NR Employment status (%) • CM 100 • Control 96 Income NR	Severity definition "Severely head injured patients" Severity GCS score, mean ± SD • CM 5.5±2.6 • Control 6.6±3.0 Duration of PTA (d), mean ± SD • CM 64.9±97.5 • Control 40.8±75.0 Time since injury NR TBI etiology (%) Traffic accident/assault/fall/other • CM ○ Traffic accident 60 ○ Assault 16	Comorbidities (%) • Respiratory ○ CM 47 ○ Control 21 • Conservative management ○ CM 16 ○ Control 31 • Tracheostomy ○ CM 32 ○ Control 16 Compensation seeking (%) • 6mo ○ CM 2 ○ Control 2 • 12mo ○ CM 0 ○ Control 6 • 24mo

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Appendix 2 (continued)

Table A2-4 (*continued*)

Study Description	Inclusion/Exclusion Criteria	Demographic/Preinjury Characteristics	TBI Characteristics	Postinjury Characteristics
Secondary outcomes • DRS • GOS		Marital status NR Military/veteran NR Insurance status NR Prior TBI NR Preexisting psychiatric conditions Alcohol intake at injury (%) • CM 36 • Control 37	○ Fall 18 ○ Other 5 • Control ○ Traffic accident 63 ○ Assault 14 ○ Fall 16 ○ Other 7 Area of brain injured NR MRI/imaging findings NR Other injury characteristics Days unconscious, mean ± SD • CM 11.3±13.5 • Control 4.6±7.5	○ CM 17 ○ Control 4 Acute rehabilitation history NR Concomitant treatment NR
Hashimoto et al[36] Study design Prospective, nonrandomized controlled trial Sample size 37 Location Kanagawa Prefecture, Japan Setting Kanagawa Rehabilitation Hospital Interventions • Comprehensive day treatment program (n=25) • Control (outpatients with TBI) (n=12) Primary outcomes • RTW • FIM/FAM • CIQ	Inclusion criteria • Near independence in activities of daily living irrespective of ability to walk or wheelchair use • The goal of returning to work or school • Having no place they were required to visit frequently except for outpatient clinic Exclusion criteria NR	Age (y), mean ± SD • Intervention 26.6±9.7 • Control 28.7±10.9 Sex (% male) • Intervention 72 • Control NR Race/ethnicity NR Education NR Employment status (% competitively employed) • Intervention 60 • Control NR Income NR Marital status NR Military/veteran NR Insurance status NR Prior TBI NR	Severity definition GCS score ≤8 Severity (%) • Intervention 76.0 • Control 83.3 Duration of PTA NR Time since injury (d), mean ± SD • Intervention 527.3±512.6 • Control 487.6±125.9 TBI etiology (%) • Intervention ○ Auto accident 20 ○ Pedestrian/auto 20 ○ Bike/auto 36 ○ Cerebral aneurysm 8 ○ Glioma 4 ○ Fall 8 ○ Work accident 4 • Control NR Area of brain injured (%) • Intervention ○ Diffuse brain injury 64 ○ Diffuse brain injury + right acute subdural hematoma 20	Comorbidities NR Compensation seeking NR Acute rehabilitation history NR Concomitant treatment NR

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Appendix 2 (continued)

Table A2-4 (*continued*)

Study Description	Inclusion/Exclusion Criteria	Demographic/Preinjury Characteristics	TBI Characteristics	Postinjury Characteristics
		Preexisting psychiatric conditions NR	○ Right acute subdural hematoma 4 ○ Subarachnoid hemorrhage 8 ○ Diffuse brain injury + contusion 4 • Control NR MRI/imaging findings NR Other injury characteristics (%) NR	
Ponsford et al[33] Study design Controlled, individually matched cohort trial Sample size 77 Location Melbourne, Australia Setting Rehabilitation center Interventions • Community-based rehabilitation (n=77) • Control (n=77) Primary outcomes RTW	Inclusion criteria Patients with moderate to severe TBI Exclusion criteria NR	Age (y), mean ± SD • Community-based 35.43±16.65 • Control 33.78±15.41 Sex (% male) • Community-based 73 • Control 73 Race/ethnicity NR Education (y), mean ± SD • Community-based 11.56±2.42 • Control 11.15±2.54 Employment status (% competitively employed) • Community-based 66 • Control 70 Income NR Marital status (% single) • Community-based 63 • Control 61 Military/veteran NR Insurance status NR	Severity, mean GCS score ± SD • Community-based 8.22±4.37 • Control 7.76±4.13 Severity definition GCS Time since injury NR TBI etiology NR Area of brain injured NR Other injury characteristics NR	Comorbidities NR Compensation seeking NR Acute rehabilitation history NR Concomitant treatment NR

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Appendix 2 (continued)

Table A2-4 (*continued*)

Study Description	Inclusion/Exclusion Criteria	Demographic/Preinjury Characteristics	TBI Characteristics	Postinjury Characteristics
		Prior TBI NR Preexisting psychiatric conditions NR		
Prigatano et al[39] Study design Retrospective, controlled cohort study Sample size 18 Location Oklahoma City, OK Setting Neuropsychologic rehabilitation program Interventions • Psychotherapeutic (n = 18) • Control (n = 18) Primary outcomes RTW	Inclusion criteria NR Exclusion criteria NR	Age (y), mean ± SD • Neuropsychologic 26.1±8.3 • Control NR Sex (% male) • Neuropsychologic 83.3 • Control NR Race/ethnicity NR Education (%) • Neuropsychologic ○ ≤12y 61.1 ○ >12y 38.9 • Control NR Employment status (% competitively employed) • Neuropsychologic 72.2 • Control NR Income NR Marital status NR Military/veteran (%) • Neuropsychologic 5.6 • Control NR Insurance status NR Prior TBI NR Preexisting psychiatric conditions NR	Severity (% moderate/severe) NR Severity definition Russell-Neurenger Average Impairment Rating Time since injury (mo) • Neuropsychologic 21.6 • Control NR TBI etiology "Severe closed head injury" Area of brain injured (%) • Neuropsychologic ○ Severe cerebral contusion 61.1 ○ Brain stem contusion 5.6 ○ Severe cerebral contusion + brain stem contusion 33.3 • Control NR Other injury characteristics (%) • Neuropsychologic ○ Posttraumatic seizure disorder 16.7 ○ Residual paresis 66.7 ○ Residual signs of aphasia and/or dysarthria 33.3 ○ "Virtually all … had cerebral contusions and/or brain stem contusion" • Control NR	Comorbidities NR Compensation seeking NR Acute rehabilitation history NR Concomitant treatment NR

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Appendix 2 (continued)

Table A2-4 (*continued*)

Study Description	Inclusion/Exclusion Criteria	Demographic/Preinjury Characteristics	TBI Characteristics	Postinjury Characteristics
Prigatano et al[34] Study design Matched control, prospective cohort Sample size 79 (outcomes for 76) Location Phoenix, AZ Setting Work Re-entry Program of the Adult Day Hospital for Neurological Rehabilitation at Saint Joseph's Hospital Interventions • Neuropsychologic rehabilitation (n=41, outcomes for 38) • Historic controls (n=38) Primary outcomes RTW	Inclusion criteria • Primary diagnosis of craniocerebral trauma or TBI • By end of study, ≥15mo elapsed since injury • Admitted to study 2–55mo from injury • All subjects considered potentially able to return to work/school Exclusion criteria NR	Age (y), mean ± SD • Neuropsychologic rehabilitation 29.6±12.7 • Historic controls 28.7±12.2 Sex (% male) • Neuropsychologic rehabilitation 68.4 • Historic controls 71.1 Race/ethnicity NR Education (y), mean ± SD • Neuropsychologic rehabilitation 13.6±2.3 • Historic controls 12.0±1.2 Employment status (% competitively employed) • Neuropsychologic rehabilitation 78.0 • Historic controls NR Income NR Marital status NR Military/veteran NR Insurance status NR Prior TBI NR Preexisting psychiatric conditions NR	Severity, mean ± SD • Neuropsychologic rehabilitation 8.08±2.7 • Historic controls (n=38) 8.03±2.8 Severity definition GCS Time since injury (mo), mean ± SD • Neuropsychologic rehabilitation 43.3±16.1 • Historic controls 33.5±8.7 TBI etiology NR Area of brain injured NR Other injury characteristics (%) • Neuropsychologic rehabilitation ○ CT/MRI findings of contusion and/or hematoma 87.7 ○ Skull fracture/no hematoma 4.9 ○ Loss of consciousness 7.3 • Historic controls NR	Comorbidities NR Compensation seeking NR Acute rehabilitation history NR Concomitant treatment NR
Rattok et al[42] Study design 3-group comparison	Inclusion criteria • Diagnosis of TBI, ≥1h coma	Age (median years) • Treatment 1: 26.8	Severity definition Severe=coma of ≥1h or cerebral anoxia of ≥12h	Prior psychiatric conditions NR Comorbidities NR

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Appendix 2 (continued)

Table A2-4 (*continued*)

Study Description	Inclusion/Exclusion Criteria	Demographic/Preinjury Characteristics	TBI Characteristics	Postinjury Characteristics
Sample size 59 Location New York, NY Metropolitan Area Setting Outpatient rehabilitation center Interventions • Treatment 1 (balanced) • Treatment 2 (interpersonal) • Treatment 3 (individualized) Primary outcomes • Cognitive performance measures • Behavioral Competence Index • Vocational	• Diagnosis of cerebral anoxia, ≥12h coma • ≥1y postinjury • Neurologic stability • Unsuccessful vocational or educational rehabilitation prior to entry into program • Residence in New York Metropolitan Area for duration of study • Age, 18—55y • Command of English • Partial independence in basic activities of self-care, ambulation, and continence • Minimum IQ of 80 on the WAIS • Minimum motivation for rehabilitation • Basic level of social appropriateness and manageability in therapeutic or training environment Exclusion criteria • History or present psychiatric complications • History of drug or alcohol abuse • History of sociopathy • Inability to communicate	• Treatment 2: 27.1 • Treatment 3: 28.5 Sex (% male) • Treatment 1: 65 • Treatment 2: 89 • Treatment 3: 61 Race/ethnicity NR Education (median years) • Treatment 1: 14.3 • Treatment 2: 13.5 • Treatment 3: 14.6 Employment status (% competitively employed) NR Income NR Marital status NR Military/veteran NR Insurance status NR Prior TBI NR	Severity (days in coma) • Treatment 1: 34.3 • Treatment 2: 38.9 • Treatment 3: 36.9 Time since injury (median months) • Treatment 1: 32 • Treatment 2: 33.8 • Treatment 3: 40.2 TBI etiology 95% acceleration/deceleration concussion; 5% cerebral anoxia MRI/imaging findings NR Other injury characteristics NR	Compensation seeking NR Acute rehabilitation history "Unsuccessful"
Salazar et al[37] Study design RCT Sample size 120 Location Washington, DC Setting US Military medical referral center Interventions • Intensive, interdisciplinary, in-hospital cognitive	Inclusion criteria • Moderate-to-severe closed head injury • Head injury within 3mo of randomization • Rancho Los Amigos cognitive level of 7 • Active-duty military member; not pending separation • Accompanied home setting with at least 1 responsible adult available • Ability to independently ambulate • No prior severe TBI or other severe disability that would preclude return to active duty after study treatment	Age Hospital = 25, 6.63 Home = 26, 6.22 Sex (% male) Hospital: 93 Home: 96 Race/ethnicity (% white) Hospital: 69 Home: 70 Education (% some college) Hospital: 41 Home: 44	Severity Severity definition GCS score≤13; or PTA≥24h; or focal cerebral contusion or hemorrhage on CT or MRI Time since injury (d), mean ± SD Hospital: 38±23.6 Home: 39±33.2 Etiology (%) MVC Hospital: 49 Home: 72	Comorbidities Headaches, violent behavior, aggressive behavior, seizures, major depression Compensation-seeking status NR Social support Accompanied home setting with at least 1 responsible adult available Acute rehabilitation history NR

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Appendix 2 (continued)

Table A2-4 (*continued*)

Study Description	Inclusion/Exclusion Criteria	Demographic/Preinjury Characteristics	TBI Characteristics	Postinjury Characteristics
rehabilitation program (hospital) (n = 30) • Limited home rehabilitation program with telephone support from psychiatric nurse (home) (n = 34) Primary outcomes • RTW • Fitness for military duty Secondary Outcomes • None	Exclusion criteria • Mild TBI	Employment status NR Income NR Marital status (% married) Hospital: 30 Home: 34 Military/veteran status (% active military) 100 Insurance status (% military coverage): 100 Prior TBI (%) Hospital: 11 Home: 18 Psychiatric conditions (% positive diagnosis) Hospital: 19 Home: 25	Assault: Hospital: 27 Home: 9 Unknown: Hospital: 24 Home: 19 Area of brain injured Cerebrum; CT or MRI Other injury characteristics (%) Closed: 100	Concomitant treatment NR
Sarajuuri et al[43] Study design Prospective cohort Sample size 39 Location Helsinki, Finland Setting Nationwide Rehabilitation Center & Neurosurgery Department within academic medical center hospital Interventions • Comprehensive (T) (n = 19) • Conventional (C) (n = 20) Primary outcome Status of productivity	Inclusion criteria • Independence in daily life and only slight physical disabilities • 16—55y of age • Completed compulsory education • Adequate potential to achieve productivity Exclusion criteria • Significant psychiatric history • Alcohol or drug abuse • Previous brain injury • Another malignant disease Population (n) T: 19 C: 20	Age (at injury; y), mean ± SD T: 30.5±10.6 C: 29.5±11.0 Sex (% male) T: 84 C: 85 Race/ethnicity NR Education (y), mean ± SD T: 11.3±2.0 C: 12.2±2.9 Employment status (preinjury; % employed or studying preinjury) T: 84 C: 85 Income NR	Severity (admission GCS score), mean ± SD (range) T: 7.9±2.7 (4—14) C: 8.2±2.5 (3—13) Severity definition NR Time since injury (mo), mean ± SD T: 66.4±17.7 C: 70.6±20.2 TBI etiology (% by mechanism) MVC/bike/pedestrian T: 63 C: 55 Assault T: 5 C: 5 Other (fall, hit by) T: 26 C: 40 Unknown T: 5 C: 0	Comorbidities NR Compensation seeking NR Acute rehabilitation history (%) OT T: 32 C: NR PT T: 47 C: NR SLP T: 26 C: NR NP T: 37 C: NR Concomitant treatment NR

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Appendix 2 (continued)

Table A2-4 (*continued*)

Study Description	Inclusion/Exclusion Criteria	Demographic/Preinjury Characteristics	TBI Characteristics	Postinjury Characteristics
		Marital status NR Military/veteran NR Insurance status NR Prior TBI NR, but prior TBI is excluded Preexisting psychiatric conditions NR, but significant psychiatric history excluded	Area of brain injured NR Other injury characteristics (%) Contusion/hematoma T: 79 C: 80 Diffuse axonal injury T: 42 C: 25 Severe intracranial pressure T: 37 C: 25 Craniotomy T: 21 C: 25	
Vanderploeg et al[38] Study design RCT, multicenter Sample size 366 Locations Minneapolis, MN; Palo Alto, CA; Richmond, VA; Tampa, FL Setting VA acute inpatient TBI rehabilitation programs Interventions • Cognitive-didactic (CD) rehabilitation therapy (n=184) • Functional-experiential (FE) (n=182) Primary outcomes • RTW Secondary outcomes • Disability Rating Scale score • Functional independence in living	Inclusion criteria • Moderate-to-severe nonpenetrating TBI within the preceding 6mo, manifested by a postresuscitation GCS score of 12 or less, or coma of 12h or more, or PTA of 24h or more, and/or focal cerebral contusion or hemorrhage on CT or MRI • RLAS cognitive level of 5–7 at time of randomization • Age 18y or older • Active-duty military member or veteran • Anticipated length of needed acute interdisciplinary TBI rehabilitation of 30d or more Exclusion criteria • History of prior inpatient acute rehabilitation for the current TBI • History of a prior moderate to severe TBI or other preinjury severe neurologic or psychiatric condition, such as psychosis, stroke, multiple sclerosis, or spinal cord injury	Age (at injury; y), mean ± SD CD: 33.2±13.5 FE: 31.7±12.9 Sex (% male) CD: 92 FE: 95 Race/ethnicity (%) Hispanic CD: 10 FE: 11 White CD: 68 FE: 69 Black CD: 20 FE: 18 Other CD: 12 FE: 12 Education (% post high school) CD: 34 FE: 37 Employment status (% working or in school) CD: 86 FE: 89 Income NR	Severity NR, but moderate/severe inclusion criteria Severity definition NR Time since injury (d), mean ± SD • CD 48.9±28.5 (n=180) • FE 51.1±29.8 (n=180) TBI etiology (%) MVC CD: 68 FE: 66 Assault CD: 10 FE: 8 Area of brain injured NR Injury characteristics • CD ○ Motor vehicular 122/180 (67.8%) ○ Fall 21/180 (11.7%) ○ Blunt object 15/180 (8.3%) ○ Sports/training accident 5/180 (2.8%)	Comorbidities NR Compensation-seeking status NR Acute rehabilitation history NR Concomitant treatment NR

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Appendix 2 (continued)

Table A2-4 (*continued*)

Study Description	Inclusion/Exclusion Criteria	Demographic/Preinjury Characteristics	TBI Characteristics	Postinjury Characteristics
		Marital status (% married) CD: 25.6 FE: 25.1 Military/veteran status (% what?) CD: 58.4 FE: 67.8 Insurance status NR Prior TBI (% "prior head injury") CD: 7.2 FE: 7.2 Preexisting psychiatric conditions NR	○ Indeterminant 17/180 (9.4%) • FE ○ Motor vehicular 119/180 (66.1%) ○ Fall 29/180 (16.1%) ○ Blunt object 9/180 (5.0%) ○ Sports/training accident 6/180 (3.3%) ○ Indeterminant 17/180 (9.4%)	
Willer et al[35] Study design Case controlled study using a matched design in a before-and-after trial Sample size 46 Location Ontario, Canada Setting Postacute residential rehabilitation program or home-based subjects Interventions • RBPR (n=23) • Control (n=23) Primary outcomes CIQ	Inclusion criteria Individuals with brain injury who had not undergone treatment in this community-based program Exclusion criteria NR	Age (y), mean ± SD • RBPR 33.42±11.31 • Control 34.76±10.72 Sex (% male) • RBPR 87 • Control 87 Race/ethnicity NR Education (%) • RBPR ○ <HS 26.0 ○ Completed HS 43.5 ○ >HS 30.4 • Control ○ <HS 26.0 ○ Completed HS 34.8 ○ >HS 39.1 Employment status NR Income NR Marital status NR Military/veteran NR Insurance status NR	Severity (% moderate/severe) All subjects were considered severe TBI Severity definition, HALS mean disability score ± SD • RBPR: 20.39±6.02 • Control: 20.30±6.09 Time since injury (y), mean ± SD • RBPR: 3.05±2.98 • Control: 4.66±4.66 TBI etiology (%) • RBPR ○ Vehicular related 95.7 ○ Assault 4.3 • Control ○ Vehicular related 95.7 ○ Assault 4.3 Area of brain injured NR Other injury characteristics Closed brain injury	Comorbidities NR Compensation seeking NR Acute rehabilitation history NR Concomitant treatment NR

(*continued on next page*)

Appendix 2 (continued)

Table A2-4 (*continued*)

Study Description	Inclusion/Exclusion Criteria	Demographic/Preinjury Characteristics	TBI Characteristics	Postinjury Characteristics
		Prior TBI NR Preexisting psychiatric conditions • RBPR: 30.4% were recruited from psychiatric hospitals • Control NR		

Abbreviations: CT, computed tomography; DRS, Disability Rating Scale; FAM, Functional Assessment Measure; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; HALS, Health and Activity Limitations Survey; HS, high school; MRI, magnetic resonance imaging; MVC, motor vehicle collision; NR, not reported; PTA, posttraumatic amnesia; RBPR, residential-based postacute rehabilitation; RLAS, Rancho Los Amigos Scale of Cognitive Functioning; WAIS, Wechsler Adult Intelligence Scale.

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