MÉMOIRE
DE DIPLÔME D'ÉTUDES SPÉCIALISÉES
EN MÉDECINE PHYSIQUE ET DE RÉADAPTATION

Par

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née le 18/03/1989

Therapeutic options for behavioral disorders following moderate-to-severe traumatic brain injury in post-acute period: cross-sectional overview and compliance with French recommendations in a cohort of 129 patients.

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Soutenu le 9 octobre 2017

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Les Capucins
Réadaptation spécialisée et soins de longue durée

ABSTRACT

Objective: To give an overview of the management of behavioral disorders following traumatic brain injury (TBI) in a cohort of 129 patients, in post-acute period, and to assess the compliance with recent recommendations of the French Society of Physical Medicine and Rehabilitation (SOFMER).

Methods: This cross-sectional regional cohort study included 129 adults suffering from moderate-to-severe traumatic brain injury, in post acute period, and referred to medical or community based facilities in our region. A structured interview of patients and proxies collected information regarding socio-demographic data and the ongoing interventions, including psychotherapy and medication. Behavioral disorders were assessed by the Behavioral Dysexecutive Syndrome Inventory (BDSI). Patients who scored above two for at least three domains of the BDSI were considered to suffer from behavioral dysexecutive syndrome (BDS). A Fisher's exact test was used to compare the interventions prescribed for patients with or without BDS.

Results: Patients were predominantly young men (mean age 26 years and 76% males) having sustained traffic accidents (78%). Forty-four percent received no interventions; 33% received psychotherapy and 43% were on pharmacological medication. 23% received medication alone with no other intervention. The prescribed medications were antidepressants (21%), neuroleptics (18%), anxiolytics (16%), mood stabilizers (14%) but no beta-blockers. Polypharmacy concerned 20% of patients. BDSI was completed for 120 patients and 85 (71%) presented current BDS. Patients with current BDS received more frequently interventions, whether psychotherapy or medication (OR=3.48, 95%CI=1.43-8.84, p=0.004), psychotherapy (OR=2.89, 95%CI=1.03-9.47, p=0.032), medications, all types combined, (OR=3.58, 95%CI=1.39-10.21, p=0.004) and antiepileptics mood stabilizers (OR=7.21, 95%CI=1.02-315.14, p=0.037).

Conclusion: Our study highlights that compliance with the current recommendations remains insufficient. Non pharmacological interventions, like psychotherapy, are inadequately implemented, although they are recommended as a first line treatment. Medications are overused, especially neuroleptics. Recommended medications, such as mood stabilizers and beta-blockers, are poorly used. Access and adherence to recommendations should be promoted.

Keywords : *traumatic brain injury, behavior, disease management, guideline adherence*

INTRODUCTION

Almost 200 to 300 people per 100,000 population are affected by traumatic brain injury (TBI) with a mortality rate of 10 to 15 per 100,000 people per year [1–4]. Survivors have to deal with long-term consequences, in which neuropsychological and behavioral impairments are the most prevalent [5–11]. Proportion of patients affected varies widely between studies, but according to a systematic literature review [9], irritability can reach 29 to 71% of TBI sufferers, agitation 46%, aggressiveness 25 to 39%, and apathy 20 to 71%. Frequency and severity of behavioral disorders is related to the initial severity of trauma [8,10,12] and they were mainly studied in moderate-to-severe TBI. They notably impact participation [7,8,13,14], including return to work [8,15], quality of life [16], and caregiver burden [17,18].

Behavioral disorders should be seen through a multidimensional framework because of dynamic nature throughout the evolution, and numerous cognitive, psychological, emotional, environmental, and social underlying factors [19,20]. They also are closely related to anosognosia, memory and concentration impairments, fatigue or pain [9,21,22]. Executive dysfunctions is now well described as one of the main mechanisms involved [6,7,23–25]. Executive dysfunction remains a broad field of research, but several authors agree in describing two types of dysfunctions: a cognitive deficit (corresponding to high level process involved in new and goal-directed tasks) and a behavioral dysexecutive syndrome (BDS) [6,7,26,27].

The management of these disorders is difficult to standardize [28]. To fill the gap, the French Society of Physical Medicine and Rehabilitation (SOFMER), in cooperation with the French High Authority for Health (Haute Autorité de Santé, HAS), created a task force to elaborate recommendations for good practice. A systematic literature review was done and 121 guidelines were formulated by professionals concerning definition, management, and follow-up of behavioral disorders [9,28–32]. They proposed a four groups framework to describe and categorize post-traumatic behavioral disorders [9]: (1) disruptive behavior by excess (including agitation, aggressiveness, irritability, hostility, verbal and physical violence, inappropriate wandering behavior, impulsiveness, screaming, bulimia, addiction, hypersexuality, exhibitionism); (2) disruptive behavior by default (including apathy, apragmatism, athymhormia, aboulia); (3) behavioral disorders secondary to depression, anxiety, and psychosis; (4) attempted suicide and suicide. A number of recommendations [13,28–31,33–37] stress the importance of a contextualized and multisource evaluation of these disorders. To complete the clinical evaluation, and standardize data collection or quantification, the use of scales is advocated. However, no particular scale was recommended by the SOFMER because of the scarcity of adequately validated French versions, the heterogeneity of literature and the metrological issues [30].

Given the available data about management, most of the recommendations, including those of the SOFMER, are based on expert consensus or studies with low level of proof [28,29,31]. Systematic reviews scarcely find high quality randomized control trial and they often include all acquired brain injuries [38–48]. Non pharmacological management of behavioral disorders are advocated as a first intention treatment, before medication,

throughout the evolution of the condition [31]. Interventions have to be specific, individualized and performed by trained professionals. Psychiatric advice [49], specific psychological care (cognitive-behavioral therapy (CBT), systemic familial therapy) [39], behavioral approaches [38] or global holistic care [39] should be used, in particular for post-traumatic anxiety [48] or depression [40,45,46]. Occupational or socio-professional activities are encouraged due to their personal structuring, socializing, and enhancing role [31]. Different approaches can be combined, and none has proven its superiority [31,38,39]. Family involvement [41] and the methods of adjustment in the relational approach [31] are well described and should be used on daily basis. Medication is a second intention treatment, and should always be associated with some of the previously mentioned strategies [29]. In behavioral disorders by excess, beta-blockers and antiepileptics mood stabilizers are recommended as a first line treatment [29]. Some literature reviews [44,49] including a Cochrane database review [42], further show that beta-blockers (pindolol, propranolol) have the highest level of proof, more particularly in agitation. However, these studies have been performed in the 90's, with small and heterogeneous samples, and without long-term follow-up [50–54]. Neuroleptics, benzodiazepines and buspirone should be used only as second line therapies, and with caution because of their increased risk of adverse effects [29]. Recommendations remain lacking in behavioral disorders by default: to check for an endocrine disorder and then opt for non pharmacological strategies is advisable; amantadine could be tried in case of persistent apathy [29]. Antidepressants have proved efficacy in post-traumatic depression [45,47] and selective serotonin reuptake inhibitors (SSRI) are advocated, especially sertraline, because of a high standard of proof, a good risk-benefit ratio, and a positive impact on brain plasticity and cognition [29,40,45].

Although SOFMER recommendations highlight the current knowledge gap and the need of further high methodological quality research on this topic [29,31,33], they are in line with the guidelines published in Scotland [35], Italy [37], Quebec [34] or the United States [13,36].

The aim of the present study was to characterize the management of behavioral disorders following moderate-to-severe TBI in a cohort of 129 patients, in post-acute period, and to compare it with recent French recommendations.

METHODS

This cross-sectional study was part of a larger regional cohort study, AVEC-TC, describing the interventions provided for people with TBI and the lay expertise of their proxies.

Population

All patients with a history of TBI seeking health or social service at the university hospital of Angers, or at one of the two specialized rehabilitation facilities of our area, or addressed either by one of the existing community based facilities or by the TBI family support group, were screened for inclusion.

Inclusion criteria were: (1) aged by 18-65 years at the time of inclusion; (2) having sustained moderate-to-severe TBI, defined by initial Glasgow coma scale (GCS) score less than 13 and/or hospitalization of at least 48 hours in intensive care; (3) being in the post-acute period of TBI, over 3 months post-injury; (4) living at home or in a nursing facility; (5) having a proxy willing to participate in data collection and complete the behavioral evaluation. Proxy could be a relative, a friend or a close professional caregiver.

Exclusion criteria were: (1) non-traumatic acquired brain injuries (such as stroke, multiple sclerosis, meningitis, hypoxic, toxic or metabolic injury); (2) mild TBI; (3) speech or language impairments precluding to complete the survey.

All eligible patients were approached, and offered to participate in the study. Informed consent was obtained from both the patient and his proxy. If applicable, the consent of the legal representative was also collected. Patients and proxies received written information on the study, and an appointment was made to collect data and complete the survey. Additional data could was retrieved from the medical file with the patient's agreement.

Data collection and outcome measures

Socio-demographic data, medical history, and type of injury

Gender, age at time of TBI and injury mechanism were collected. Injury mechanism was classified as traffic accidents, domestic accidents or other (sport accident, physical assault or unknown). Significant medical history, previous brain injury, and psychiatric history were noted. Psychiatric history was defined by previous follow-up by a psychologist or a psychiatrist, psychotropic treatment or hospitalization in Psychiatry. TBI severity was defined by initial GCS score, approximate duration of loss of consciousness (LOC), duration of posttraumatic amnesia (PTA), and Glasgow outcome scale (GOS) [55]. Injury type was classified as focal lesions (local intracerebral hemorrhage or contusion, and extraparenchymal hematoma) or multifocal lesions, including diffuse axonal injury.

Non pharmacological and pharmacological interventions

Non pharmacological interventions included psychotherapies conducted by a psychologist or a psychiatrist. Type of sessions (individual or family), frequency (ranged from

less than once a year to more than five times a week), and the year of the onset of the psychotherapy were recorded.

Pharmacological treatments were categorized into neuroleptics, antiepileptics mood stabilizers, antidepressants, anxiolytics, beta-blockers, hypnotics, ritaline, amantadine, and buspirone. Antiepileptics mood stabilizers included valproic acid derivatives (sodium valproate and divalproate, valpromide), carbamazepine and oxcarbazepine. Antidepressants were classified as selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCA), and atypical antidepressant (mirtazapine, mianserine, and agomelatine). The data were obtained from patient or proxy declarations, or written prescriptions if available. Polypharmacy was defined as the concurrent prescription of two or more medications.

Behavioral impairments

Behavioral disorders were assessed by proxies using the Behavioral Dysexecutive Syndrome Inventory (BDSI). BDSI is a hetero-evaluation that is part of the GREFEX (Groupe de Réflexion pour l'Evaluation des Fonctions Exécutives) battery [6,7]. This is a structured proxy interview assessing twelve domains: (1) reduction of activities (hypoactivity with apathy-aboulia, avolition); (2) difficulties for anticipation, planning, and initiation of activities; (3) disinterest and indifference to his/her own concern and others; (4) euphoria, joviality, emotional lability, and moria; (5) irritability, aggressiveness; (6) hyperactivity, distractibility, impulsivity, psychomotor instability; (7) stereotyped and perseverative behavior; (8) environmental dependency; (9) anosognosia-anosodiaphoria; (10) confabulations; (11) social behavior disorders; (12) sexual, sphincter control, and eating disorders. For each domain, proxy has to state if there was a change in comparison to the preinjury state. If so, he also has to rate severity (range from 1 to 3), frequency of occurrence (range from 1 to 4), and the burden induced by the disorder. Two scores are computed for each questionnaire: a global score (frequency × severity, range from 1 to 12), and a resounding score (range from 0 to 5). A domain is positive if global score and/or resounding score is strictly greater than 2. Participants with at least 3 impaired domains are considered to suffer from BDS. To be considered as dysexecutive, behavioral disorders should not be further explained by other cognitive, psychiatric or sensorimotor disorders, and must lead to significant changes in daily life and compared to preinjury state [6,7].

Statistical analysis

Variables were entered under Epidata® and processed by Excel®. Descriptive statistics were used to characterize the population, and data were expressed as mean and standard deviation (SD) or number of patients and rounded percentage (%) of the total sample. For each intervention, the prevalence was computed as the ratio between the number of patients concerned and the total of patients.

In secondary analysis, a Fisher's exact test was performed to compare the prevalence of interventions according to the presence of BDS. A p-value < 0.05 was deemed as statistically significant. Results were expressed as Odds Ratio (OR) with 95% confidence interval

(95%CI). Statistical analysis were performed using the free French tools BiostaTGV available on http://marne.u707.jussieu.fr/biostatgv/ (calculations via statistical software R).

Ethical aspects

This observational study was approved by the local ethical research committees and the independent protection to person committee of University Ouest II, Angers, on 25 January, 2013, and authorized by the National Authority for Health on 29 January, 2013. This research was completed in accordance with the French law n°2004-806 and the Helsinki Declaration. Written and oral information was given to patients and their proxies. Written consent was obtained from all participants (patients, caregivers and legal guardian when appropriate).

RESULTS

Population (Table I)

One hundred and twenty-nine patients completed the questionnaire. Full BDSI questionnaires were available for 120 patients (93%) (Figure 1). Ninety-eight of the 129 patients were males (76%). Mean age at time of TBI was 26 years (SD=13), ranged from 2 to 70 years, based on the available data (n=128 subjects). One hundred and sixteen patients (90%) had an initial GCS under 9 (severe TBI), and 8 (6%) between 9 and 12 (moderate TBI), based on the available data (n=125). Mean delay between TBI and evaluation was 13 years (SD=11), ranged from 3 months to 54 years, based on the available data (n=128). Main mechanism was road traffic accident in 101 patients (78%) with diffuse injuries in 109 (85%), based on the available data (n=115). Regarding GOS, 13 patients (10%) experienced good recovery, 41 (32%) moderate disability, and 75 (58%) severe disability.

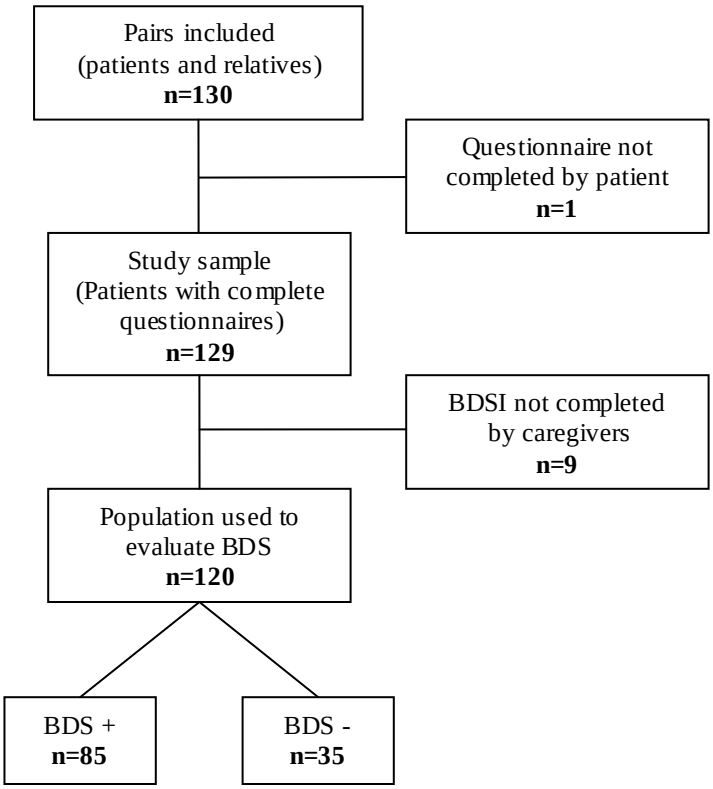

Figure 1. Flowchart of the study population.

BDSI: Behavioral Dysexecutive Syndrome Inventory; BDS: Behavioral Dysexecutive Syndrome

Table I. Characteristics of the study population: total sample (n=129), and subjects with (n=85) and without (n=35) behavioral dysexecutive syndrome (BDS).

Patients' characteristics	Study sample	*Missing Data*	BDS +	*Missing Data*	BDS -	*Missing Data*
	Mean +/- standard deviation (minimum - maximum) or Count (%)					
BDS						
Present	85 (65.89%)	*9*	-	-	-	-
Absent	35 (27.13%)	*(6.98%)*				
Gender						
Female	31 (24.03%)	*0*	23 (27.06%)	*0*	6 (17.14%)	*0*
Male	98 (75.97%)		62 (72.94%)		29 (82.86%)	
Age at time of TBI (years)	26.07 +/- 13.04 (2.04 - 70.28)	*1 (0.78%)*	26.36 +/- 12.65 (2.04 - 60.98)	*1 (1.18%)*	26.84 +/- 13.64 (7.57 - 70.28)	*0*
Delay between TBI and evaluation (years)	12.62 +/- 11.43 (0.26 - 53.82)	*1 (0.78%)*	12.19 +/- 10.96 (0.38 - 38.33)	*1 (1.18%)*	12.80 +/- 13.29 (0.26 - 53.82)	*0*
Medical history	23 (17.83%)		19 (22.35%)		3 (8.57%)	
Epilepsy	1 (0.78%)		1 (1.18%)		0	
Mild intellectual disability	1 (0.78%)		1 (1.18%)		0	
Previous TBI	8 (6.20%)	*0*	6 (7.06%)	*0*	2 (5.71%)	*0*
Other brain injury	0		0		0	
Psychiatric history	13 (10.08%)		11 (12.94%)		1 (2.86%)	
TBI severity						
Moderate	8 (6.20%)	*5*	6 (7.06%)	*4*	2 (5.71%)	*0*
Severe	116 (89.92%)	*(3.88%)*	75 (88.24%)	*(4.71%)*	33 (94.29%)	
Injury type						
Focal	6 (4.65%)	*14*	3 (3.53%)	*9*	1 (2.86%)	*2*
Diffuse	109 (84.50%)	*(10.85%)*	73 (85.88%)	*(10.59%)*	32 (91.43%)	*(5.71%)*
Injury mechanism						
Traffic accident	101 (78.29%)	*0*	67 (78.82%)	*0*	26 (74.29%)	*0*
Domestic accident	11 (8.53%)		7 (8.24%)		4 (11.43%)	
Other	17 (13.18%)		11 (12.94%)		5 (14.29%)	
Duration of LOC (days)	32.25 +/- 34.95 (0 - 183)	*19 (14.73%)*	32.34 +/- 32.48 (0 - 180)	*12 (14.12%)*	24.38 +/- 21.91 (0 - 90)	*6 (17.14%)*
Duration of PTA (days)	85.86 +/- 102.85 (0 - 700)	*65 (50.39%)*	97.40 +/- 117.17 (0-700)	*40 (47.06%)*	61.78 +/- 47.55 (3 - 150)	*17 (48.57%)*
Glasgow Outcome Scale:						
Good recovery	13 (10.08%)		6 (7.06%)		5 (14.29%)	
Moderate disability	41 (31.78%)	*0*	26 (30.59%)	*0*	12 (34.29%)	*0*
Severe disability	75 (58.14%)		53 (62.35%)		18 (51.43%)	
Persistent vegetative state	0		0		0	

BDS: Behavioral dysexecutive syndrome, present (+) or not (-); TBI: Traumatic brain injury; LOC: Loss of consciousness; PTA: Posttraumatic amnesia.

Medical and social support, and environment

Proxies were spouses or husbands (current or former) for 30 patients (25%), parents (mothers or fathers) for 51 (43%), brothers or sisters for six (5%), children for two, friend for one, and professional caregivers for 30 patients (25%). Professional caregivers were paramedics, educational or social workers.

Forty-two patients (33%) received or have received home based specialized medical and social support; 40 patients (31%) benefited or have benefited from a community based vocational counseling program; 8 patients (6%) benefited or have benefited from community based psychiatric service. Twenty-seven patients (21%) lived in a nursing facility, 29 (22%) were hosted by a close relative, and 73 (57%) lived alone in ordinary home environment. Among the 102 patients who did not live in a nursing facility, 56 (55%) required the intervention of professional caregivers, and 76 (75%) required the help of relatives in daily life activities. Sixty patients (47%) benefited from a legal protection measure while none of them did before the TBI.

Forty-seven patients (36%) received rehabilitation: cognitive rehabilitation (speech therapy or neuropsychology) for 43 of them (33%), and occupational therapy for 22 (17%).

Psychotherapy and pharmacological interventions in the study sample (Table II**)**

Fifty-seven patients (44%) received no intervention. Forty-two patients underwent psychotherapies (33 %): 40 of them (95%) were individual and the two others were family therapies. The frequency of psychotherapy was less than once a month for 4 patients (10%), at least once a month for 25 patients (60%), and at least once a week for 9 patients (21%), based on the available data (n=125). The mean duration of psychotherapies was 9.5 years (SD=9.9), ranged from 0 to 41 years, based on the available data (n=121).

Fifty-six patients (43%) received pharmacological treatment: antidepressants for 27 of them (21%), neuroleptics for 23 (18%), anxiolytics for 20 (16%), and antiepileptic mood stabilizers for 18 (14%). Among the 23 neuroleptics prescriptions, 21 (91%) were monotherapy; 12 (52%) were second generation neuroleptic. Among the 27 antidepressants prescriptions, 21 (78%) were SSRI or SNRI, 2 (7%) were TCA, and 5 (19%) were atypical antidepressants. Two patients received buspirone and none received beta-blockers or amantadine. Twenty-six patients were polymedicated (20%) and these patients were taking a mean of 2.5 (SD=0.8) medications, ranging from 2 to 5 medications.

Thirty patients (23%) were on medication and received no psychotherapy (Figure 2). Twenty-six (20%) received both psychotherapy and medications.

Table II. Interventions in the study sample (n=129).

	Number of patients	Percentage
No intervention	57	44.19%
Psychotherapy	42	32,56%
Pharmacological intervention	56	43,41%
Antidepressants[1]	27	20,93%
SSRI	14	10.85%
SNRI	7	5.43%
TCA	2	1.55%
Atypical antidepressants	5	3.88%
Neuroleptics[2]	23	17,83%
First generation	11	7.75%
Second generation	13	9.30%
Several neuroleptics	2	1.55%
Anxiolytics	20	15,50%
Mood Stabilizers	18	13,95%
Hypnotics	5	3,88%
Buspirone	2	1,55%
Beta-blockers	0	0.00%
Amantadine	0	0.00%
Polypharmacy	26	20.16%

SSRI: Selective serotonin reuptake inhibitors; SNRI: Serotonin-norepinephrine reuptake inhibitors; TCA: Tricyclic antidepressants; Atypical antidepressant: mirtazapine, mianserine, and agomelatine.

[1]One patient received two antidepressants (SNRI and atypical).

[2]Of the two patients who received several neuroleptics, one received two second generation neuroleptics, and the other had first and second generation neuroleptics.

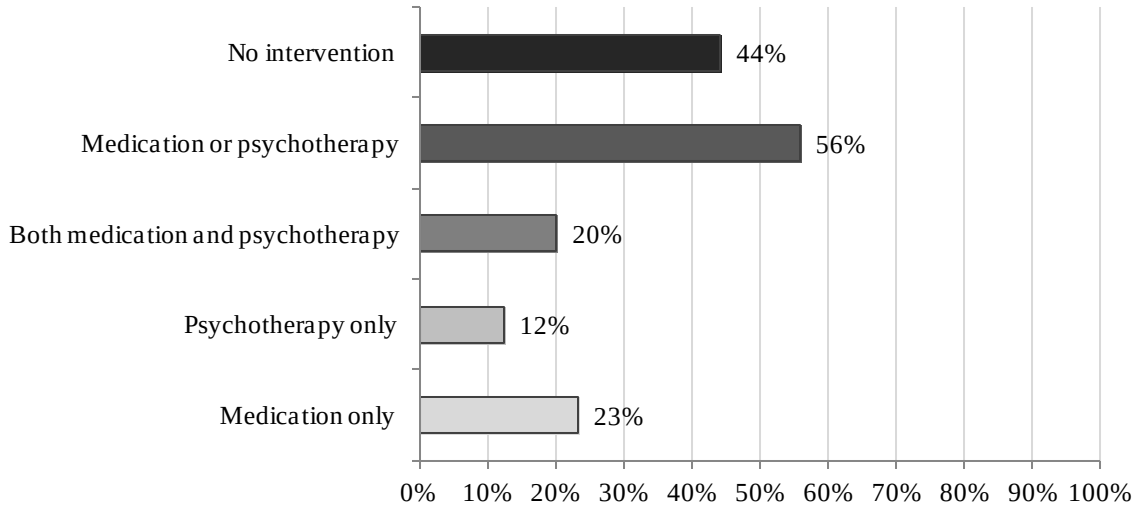

Figure 2. Repartition of patients according to the type of interventions, psychotherapy or medication, in the study sample (n=129).

Interventions according to the behavioral dysexecutive syndrome

Among the 120 patients with available BDSI assessment, 85 patients (71%) were considered to suffer from current BDS. The most impaired domains were difficulties in anticipation (65%), reduction of activities (56%), disinterest and irritability (53%), followed by anosognosia (43%) and hyperactivity (38%) (Figure 3).

Patients presenting current BDS were more likely to receive interventions, whether psychotherapy or medication (Odds Ratio OR=3.48, 95% confidence interval 95%CI=1.43-8.84, p=0.004), than subjects without BDS **(**Table III). This significant difference remained true for psychotherapy (OR=2.89, 95%CI=1.03-9.47, p=0.032) or any type of medication (OR=3.58, 95%CI=1.39-10.21, p=0.004). They also received more antiepileptics mood stabilizers (OR=7.21, 95%CI=1.02-315.14, p=0.037). There was no significant difference between the two groups in receiving other medications.

There was no statistically significant difference in receiving only medications without psychotherapy, between patients presenting current BDS or not (p=0.35) (Figure 4).

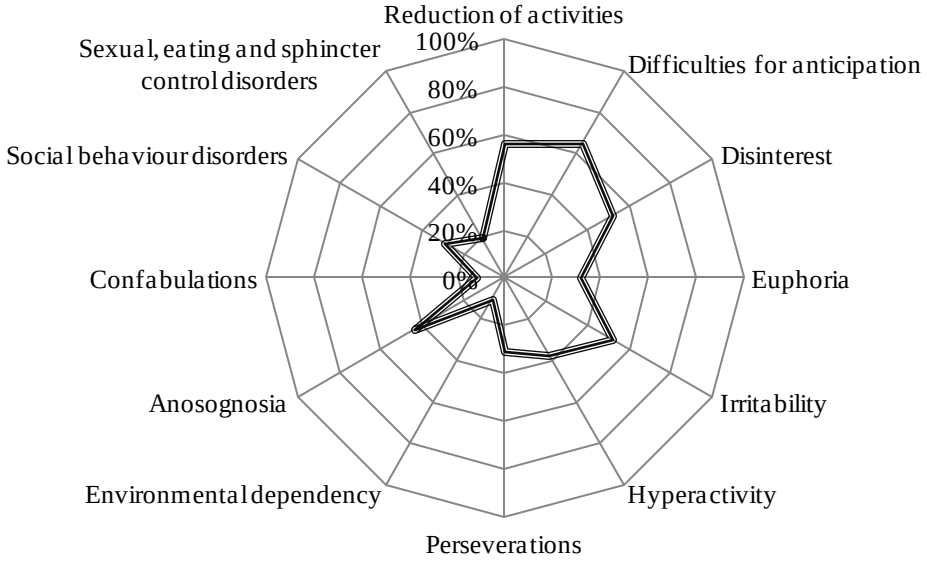

Figure 3. Domains impacted in patients with behavioral dysexecutive syndrome (n=85), according to the Behavioral Dysexecutive Syndrome Inventory.

Table III. Comparison of interventions, in number of patients and percentage (%), between patients with (+) or without (-) behavioral dysexecutive syndrome (BDS).

	BDS +	**BDS -**	***p-value***	**Total**
No intervention	30 (35.29%)	23 (65.71%)	***0.004****	53 (44.17%)
Intervention	55 (64.71%)	12 (34.29%)	***0.004****	67 (55.83%)
Psychotherapy	32 (37.65%)	6 (17.14%)	***0.032****	38 (31.67%)
Psychotropics medication	44 (51.76%)	8 (22.86%)	***0.004****	52 (43.33%)
Neuroleptics	19 (22.35%)	4 (11.43%)	*0.208*	25 (20.83%)
Mood stabilizers	15 (17.65%)	1 (2.86%)	***0.037****	16 (13.33%)
Antidepressants	20 (23.53%)	4 (11.43%)	*0.208*	24 (20.00%)
Anxiolytics	16 (18.82%)	3 (8.57%)	*0.270*	19 (15.83%)
Polypharmacy	20 (23.53%)	4 (11.43%)	*0.208*	24 (20.00%)
Numbers of patients	85	35	-	120

*significant p-value < 0.05 (evaluate by a Fisher's exact test)

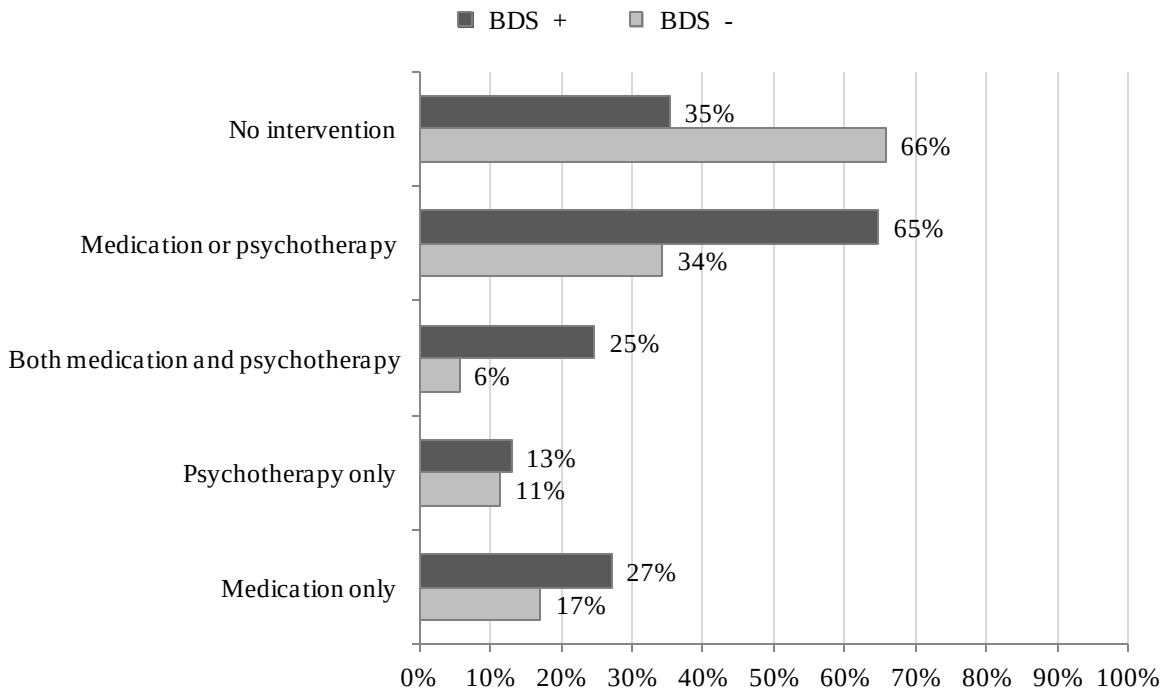

Figure 4. Proportion of patients (in percentage (%) of each sample) according to the type of interventions, psychotherapy or medication, with (+) or without (-) behavioral dysexecutive syndrome (BDS).

DISCUSSION

This cross-sectional study is, to our knowledge, the first of its design characterizing the management of behavioral disorders, in a large cohort of patients with moderate-to-severe TBI in post-acute period, and comparing it with recent French recommendations.

Evaluation of behavioral disorders

According to the BDSI, behavioral disorders concerned almost three quarters of our patients, which is consistent with the literature [9]. Using the same scale, Azouvi *et al.* [6] found about 80% of BDS in their population of severe TBI, with a similar distribution in the domains of the BDSI.

Limitations should be stated regarding the completeness and applicability of this study. First, data did not include information on the evolution of behavioral disorders over time, and did not assess the confounding factors [19,20]. Inclusion criteria may have led to over or underestimation of BDS. Indeed, they selected a large number of patients living in nursing facilities or hosted by a proxy (43%). In addition, they excluded patients not in contact with the health system or socially isolated. However, this bias is inherent to the assessment of TBI patients with neuropsychological disorders, leading to difficulties in the follow-up. The last limitation comes from the use of the BDSI to assess behavioral disorders. A multisource evaluation, based on direct observation of the patient by professionals, hetero-evaluation by proxies, and self-evaluation by patients themselves, is recommended [30]. Such an assessment would not have been workable in our large cohort. Advantages of the BDSI are to be specific to TBI, to compare subjects to their previous state and to be validated in French. The similarity with the description used by the SOFMER [9] was also useful in comparing the date to the recommendations. Hetero-evaluation may lead to overestimation or underestimation [6]. Nevertheless, behavioral disorders are rather described by proxies and often neglected by patients because of cognitive impairment or anosognosia.

Non pharmacological interventions

One third of our patients underwent psychotherapies, and patients with current BDS were more concerned than those without current BDS (OR=2.9). Given the significance and frequency of behavioral disorders, this prevalence remains quite low. Because of neuropsychological disorders, psychotherapies can be difficult to implement after TBI and need to be adapted to each patient [56]. In the present study, consultations were infrequent and run over prolonged periods of time. This suggests some kind of psychological follow-up rather than implementation of specific psychotherapies, especially CBT therapies. These latter are among the most recommended psychotherapies, particularly in English-speaking literature [31,34,35,40,46,57], but they are not widely used in France [11].

Family therapies were uncommon in our cohort with two patients concerned. However, support and involvement of families are recommended in order to reduce the associated burden, and allow them to play a part in the management of behavioral disorders [31,41,58].

This study did not have specific data on the use of global approaches, such as holistic programs. The development and spread of this multifaceted and progressive support need to be promoted [31].

Almost a quarter of our patients received medication without associated psychotherapy, highlighting their underutilization. Health professionals, together with family and patients, face a real challenge in improving, making available and implementing non pharmacological interventions.

Pharmacological interventions

Almost half of our patients had medications, and patients with current BDS received more frequently medications (OR=3.6). An extensive use of psychotropics has been described by other authors in rehabilitation inpatients [59,60] or outpatients many years after TBI [61]. In our study, antidepressants were the most frequently prescribed medication. The use of antidepressants is widespread in France [62,63]. Nevertheless, it does not exceed 2 to 6% of the general population [63–65] compared to more than 20% in our cohort. This should be related to a prevalence of depression 7.5 times higher after TBI than in the general population [9].

Although recommended as first line treatments [29], mood stabilizers ranked only fourth in terms of frequency of prescription. Appropriately, they were more frequently prescribed in patients with BDS (OR=7.21, to be weighted by a broad confidence interval). No patient was on beta-blocker, although they have the highest level of evidence in the treatment of post-traumatic agitation [44,49,66]. Unclear mechanism of action, lack of experience of clinicians, and concerns about cardiovascular adverse effects may have limited the prescriptions of beta-blockers [44,67]. In contrast, prescriptions of neuroleptics and anxiolytics represented more than a quarter of patients (35 patients (27%) received anxiolytic and/or neuroleptic). Duration of the prescriptions was not specified but medications were taken daily and not punctually as recommended. Indeed, these treatments should be reserved for acute agitation or aggressiveness, to obtain quick sedation [29]. This overuse of neuroleptics and anxiolytics is probably related to old prescription habits inherited from psychiatry [68]. Recommendations now insist on adverse effects, particularly for first generation neuroleptics [29].

Half of the patients receiving medication were polymedicated with more than two treatments. This result is consistent with the study by Cosano *et al.* where more than 80% of inpatients received psychotropic drugs, and at least two medications for two thirds of them [60]. Limiting polymedication seems to be the first battleground to tackle because of the increased sensitivity to drug in TBI sufferers [60].

Compliance with recommendations

A suboptimal adherence to recommendations had already been noted at the very acute period of TBI management [69]. The lack of adherence to the recommendations of the SOFMER can be explained by several factors.

First, recommendations are recent and level of proof is low, mainly expert consensus [28], while recommendations with a higher level of evidence are more often followed [69].

Then, access to recommended interventions may be difficult, both for psychotherapies which must be adapted [56], and for medications that do not have marketing authorization in this indication [59]. Prescription therefore requires a multidisciplinary assessment of the risk-benefit ratio, strict compliance with prescribing rules, and close monitoring of adverse effects or interactions.

Finally, the specialization of the physicians involved in the follow-up must be examined. According to the recommendations, the management of behavioral disorders has to be carried out by therapists specialized in TBI [31]. Francisco *et al.* shows a difference in drug preference between specialist and non-specialist physicians [67], with a better compliance with recommendations for specialists. Physicians must have a strong knowledge of TBI, of patient's particular situation and environment. Sufficient time should be devoted to the assessment of the situation, in order to select the most appropriate intervention, and reassess it on a regular basis. Since resorting to specialist physicians may be difficult, access to the recommendations for general practitioners and local stakeholders is crucial.

CONCLUSION

Often referred as invisible, long lasting behavioral disorders are not at all invisible to patients, relatives, and healthcare community. They represent a real challenge since neither evaluation nor therapeutic interventions are standardized, but recommendations provide guidelines to help clinicians in addressing the complexity of their management. The present study gives an overview of non pharmacological and pharmacological interventions implemented in a cohort of 129 patients, in post-acute period following TBI. It highlights that recommendation to use non pharmacological interventions as a first line treatment remains frequently not implemented. Recommended medications such as mood stabilizers and beta-blockers remain less frequently prescribed compared to neuroleptics or anxiolytics, which are not recommended as first line treatments. Compliance with recommendations and access to non pharmacological interventions must be promoted.

Acknowledgements

The project AVEC-TC was funded by the University Hospital of Angers and the International Foundation of Applied Disability Research (FIRAH).

Authors want to thank TBI sufferers, family, and carers, for their participation and implication. They also want to thank the French family association UNAFTC (Union Nationale des Associations de Familles de Traumatisés Crâniens et Cérébro-lésés), and all the professionals involved in the center Les Capucins in Angers, the center L'Arche in Le Mans, Arceau Anjou's services and establishments in Angers.

Declaration of interest

Authors report no conflicts of interest. They are all responsible for content and writing of the paper.

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