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Review

Drugs for behavior disorders after traumatic brain injury: Systematic review and expert consensus leading to French recommendations for good practice

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ABSTRACT

Objective: There are no handbook or recommendations for the use of pharmacological agents to treat neurobehavioral disorders after traumatic brain injury (TBI). This work proposes a systematic review of the literature and a user guide on neuroleptics, antidepressants, beta-blockers, mood stabilizers and other medications for irritability, aggressiveness, agitation, impulsivity, depression, apathy...
Method: Steering, working and reading groups (62 people) were formed under the control of the French High Authority for Health (HAS) in collaboration with the SOFMER scientific society (French Society of Physical and Rehabilitation Medicine). Articles were searched by HAS officers in the Medline database from 1990 to 2012, crossing TBI and pharmacological agents. The HAS method to select, read and analyze papers is close to the PRISMA statements.
Results: Out of 772 references, 89 were analyzed, covering a total of 1306 people with TBI. There is insufficient evidence to standardize drug treatments for these disorders. There are however some elements to establish consensus recommendations for good clinical practice. Propranolol can improve aggression (B grade). Carbamazepine and valproate seem effective on agitation and aggression and are recommended as first line treatment (Expert Consensus [EC]). There is no evidence of efficacy for neuroleptics. Their prescription is based on emergency situation for a crisis (loxapine) but not for long-term use (EC). Antidepressants are recommended to treat depression (EC) with a higher standard of proof for Selective Serotonin Reuptake Inhibitors (SSRI, grade B). Other products are described.
Conclusion: The choice of treatment depends on the level of evidence, target symptoms, custom objectives, clinical experience and caution strategies.

1. Introduction

Behavioral disorders after traumatic brain injury (TBI) represent the main impairment for patients after their accident [1,2]. The care management of these behavioral disorders is highly relevant for families and society. Behaviors, such as agitation, opposition, disinhibition, irritability, impulsiveness, bulimia, hypersexuality, Kluver and Bucy Syndrome, hostility, aggressiveness, verbal and physical violence, anxiety and depression (see Stephan et al. in this issue) require the consensus from experts who understand the specific characteristics of people with TBI. The pharmacological approach is highly specialized and is based on a comprehensive clinical experience. The most recent data from international literature suggest using beta-blockers, neuroleptics, antiepileptics, antidepressants, benzodiazepines, amantadine and other drugs.

The SOFMER French Society of Physical Medicine and Rehabilitation under the auspices of the French High Authority for Health (HAS) decided to elaborate recommendations of good practice (RGP), in response to the announcement in 2010 of a specific government action plan for patients with TBI. Through a systematic review of the literature, the objective of this work was to organize care pathways, provide a practical care management guide and

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improve the effectiveness of therapeutic modalities. These recommendations concern adult patients with traumatic brain injury presenting with behavioral disorders in the acute and chronic post-traumatic stages. These patients are still hospitalized or living at home or in an institution. The professionals concerned are physicians, healthcare personnel from the units caring for these patients, personnel of medico-social institutes or specialized care networks.

The population of patients with TBI is more sensitive to pharmacological treatments, it is a particular population and it deserves specific studies that are difficult to implement in randomized, double-blind vs. placebo protocols. Multicenter studies are often necessary to obtain a sample of patient large enough and homogeneous to obtain sufficient statistical power (e.g. age, time since injury, identical measure scales and identical concept definitions). Almost all systematic review studies, controlled or not-controlled studies and original studies come to the conclusion that further studies with a better methodology are needed. The relevance of this work is a dual one. On the one hand, proposing a systematic review of the literature to provide therapeutic solutions according to the available level of evidence and on the other hand bring consensus expert opinions when studies are insufficient to draw a conclusion.

2. Methodology

According to HAS criteria, the methodology involved a total of 62 people divided into 3 working groups, and 4 stages:

- elaboration of a framework letter with questions developed by the Steering committee (6 people: 3 professors of PM&R, 1 lawyer, 1 director of a medical structure);
- selection, analysis of the scientific literature and elaboration of a scientific rationale by the project managers (8 people: 1 librarian, 2 HAS physicians, 1 PM&R professor, 4 PM&R physicians);
- the elaboration of recommendations, based on the scientific rationale, by a working group (23 people: 5 project leaders PM&R physicians, 3 psychologists, 2 people representing families, 4 PM&R physicians, including 1 professor, 4 psychiatrists, 1 director of a medical structure, 1 professor of physical education, 1 MDPH (Departmental Home for Disabled Persons) physician, 1 social worker, 1 lawyer);
- the critic analysis of all proposals by a reading group (30 people: 7 psychologists, including 3 professors, 10 PM&R specialists, including a professor, a magistrate, a lawyer, a physiotherapist, a social worker, 2 healthcare managers, 2 people representing the families, one person representing the insurance companies, one director of a medical structure, a psychiatrist, a physician working in the prison system).

The HAS methodology is explained in details in this special issue, in the editorial (see Mathé and Luauté). This editorial reports 6 questions, our work focuses on drug therapeutics.

The literature research was performed by the HAS literature research team using as the main database Medline over the 1990–2012 period. Some additional articles related to the final selection but anterior to 1990 were also analyzed. Literature search strategies are detailed in Box 1. A complimentary search was performed covering the period up to June 2015 without using the HAS research team. Each article selected was analyzed according to the literature review methodology using reading grids in order to attribute to each article a scientific level of evidence [3]. According to the level of evidence of the studies on which they recommendations are based, they have a variable grade, scored from A to C, see Table 1.

Box 1. Literature search strategy for all types of studies.

(''Brain Injuries'' (Majr: NoExp) OR ''Craniocerebral Trauma'' (Majr: NoExp) AND ''Drug Therapy'' (Mesh) Or ''Central Nervous System Stimulants'' (Mesh) OR ''Methylphenidate'' (Mesh) OR ''Dopamine Agents'' (Mesh) OR ''Dopamine'' (Mesh) OR ''Amantadine'' (Mesh) OR ''Dopamine Agonists'' (Mesh) OR ''Bromocriptine'' (Mesh) Or ''Levodopa'' (Mesh) OR ''Antidepressive Agents'' (Mesh) OR ''Sertraline'' (Mesh) OR ''Fluoxetine'' (Mesh) OR ''Paroxetine'' (Mesh) OR ''Citalopram'' (Mesh) OR ''tianeptine'' (Supplementary Concept) OR ''Trazodone'' (Mesh) OR ''Amitriptyline'' (Mesh) OR ''Clomipramine'' (Mesh) OR ''Trimipramine'' (Mesh) OR ''Mianserin'' (Mesh) OR ''mirtazapine'' (Supplementary Concept) OR ''milnacipran'' (Supplementary Concept) OR ''duloxetine'' (Supplementary Concept) OR ''Iproniazid'' (Mesh) OR ''venlafaxine'' (Supplementary Concept) OR ''Cholinesterase Inhibitors'' (Mesh) OR ''Physostigmine'' (Mesh) OR ''donepezil'' (Supplementary Concept) OR ''rivastigmine'' (Supplementary Concept) OR ''Adrenergic beta-Antagonists'' (Mesh) OR ''Propranolol'' (Mesh) OR ''Haloperidol'' (Mesh) OR ''Methotrimeprazine'' (Mesh) OR ''Clozapine'' (Mesh) OR ''quetiapine'' (Supplementary Concept) OR ''ziprasidone'' (Supplementary Concept) OR ''Anticonvulsants'' (Mesh) OR ''Valproic Acid'' (Mesh) OR ''Carbamazepine'' (Mesh) OR ''lamotrigine'' (Supplementary Concept) OR ''Lithium'' (Mesh) OR ''zolpidem'' (Supplementary Concept) OR ''modafinil'' (Supplementary Concept) OR ''Brain Injuries/drug therapy'' (Majr) OR ''Craniocerebral Trauma/drug therapy'' (Majr) AND ''Meta-Analysis as Topic'' (Mesh) OR ''Meta-Analysis'' (Publication Type) OR ''Review Literature as Topic'' (Mesh) OR Meta-Analysis OR Review Literature Or Quantitative Review OR ''Random Allocation'' (Mesh) OR ''Randomized Controlled Trials as Topic'' (Mesh) OR ''Randomized Controlled Trial'' (Publication Type) OR Random*'' (Title) OR''Comparative Effectiveness Research'' (Mesh) OR ''Comparative Study'' (Publication Type) Or compar*(title) NOT ''Critical Care'' (Mesh) OR ''Child'' (Mesh) OR ''Infant'' (Mesh) OR ''Pediatrics'' (Mesh) OR ''Adolescent'' (Mesh) Or Critical care OR child* OR infan* Or paediatr* or pediatr* OR adolescent*.

Table 1
Grade recommendations.

Level of scientific evidence provided by the literature (treatment studies)	Grade recommendation
Level 1	Established scientific evidence
High power randomized comparative trials	A
Meta-analysis of randomized controlled trials	
Decision analysis based on well-conducted studies	
Level 2	Scientific presumption
Low-power randomized comparative trials	B
Non-randomized comparative studies well-conducted	
Cohort studies	
Level 3	Low level of evidence
Case-control Studies	C
Level 4 (NP4)	
Comparative studies with considerable bias	
Retrospective studies	
Case series	

Each selected item was analyzed according to the principles of critical literature reading. Based on this literature review, the working group proposed, whenever possible, recommendations. Depending on the level of evidence of studies on which they are based, the recommendations have a varying degree, from A to C according to the scale proposed by the HAS. In the absence of studies, the recommendations are based on a professional consensus (EC, Expert Consensus Working Group).