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Original Article

Pharmacological treatment of neurobehavioural sequelae of traumatic brain injury

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Summary

Neurobehavioural sequelae of traumatic brain injuries require an appropriate/effective pharmacological response in that they represent an important cause of disability. In this field, there is no evidence that reaches the level of a standard: there are guidelines on the use of methylphenidate, donepezil and bromocriptine for the treatment of cognitive disturbances, for the non-use of phenytoin and for the use of β-blockers for controlling aggressiveness. Resolving a single symptom is not relevant in a rehabilitation project if it is not in the context of a more complex picture of neurobehavioural recovery, in which the positive and negative effects of every therapeutic choice are considered. For example, phenytoin could be used for the positive control of epileptic crises but is not advised since it impedes the recovery of cognitive functions in general. Analogous effects not yet identified may concern benzodiazepine, neuroleptics and other sedatives usually prescribed in cases of cranial trauma. Psychotropic drugs are considered to be able to influence the neuronal plasticity processes. Studies on animals have shown that the administration of D-amphetamine combined with sensorial-motor exercise produces the steady acceleration of motor recovery, which acts as a catalyst to the neurological recovery process. On the other hand, α_1-NA receptor antagonist drugs produce negative effects; these include clonidine (antihypertension) and haloperidol (neuroleptic). Studies need to be carried out to evaluate the effectiveness of particular drugs. These studies need to focus not only on the disappearance of symptoms but also on the positive and negative effects on overall rehabilitation and on the neurobiological recovery of the patient.

Keywords: BRAIN INJURY; PSYCHOSIS; TRAUMA; DEPRESSION; LONG-TERM EFFECTS; COGNITION DISORDERS.

Guidelines for the treatment of neurobehavioural sequelae

Neurobehavioural sequelae of traumatic brain injury (TBI) require appropriate/effective pharmacological intervention and are known to be an important cause of disability [1] in that

1. they impede rehabilitation and the recovery process as a whole;
2. they contribute to a sub-optimal follow-up;
3. they impede re-establishing family and work relationships.

They have a serious impact on patients' lives because they may cause family crises, reduction in quality of life and loss of productivity [2].

A recent publication of guidelines [3] for the pharmacological treatment of neurobehavioural disturbances following traumatic brain lesions identifies three broad categories of the problem: *psychiatric disturbances, cognitive problems and aggressiveness*.

The most frequent *psychiatric disturbances* found in patients are anxiety and depression, isolated or

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together, and less frequently there are real psychotic syndromes [4].

The most frequently encountered *cognitive disturbances*, in great synthesis, are *attention/concentration deficits and the speed of mental elaboration*, manifested in the inability to concentrate, distractibility, difficulty in understanding more than one task at a time, confusion and perplexity in thought, tiredness and increased time and effort in carrying out simple tasks [5,6] and *memory deficit*, with loss in the processes of codification and recall of information [7]; as well as *disturbances of execution* functions like reasoning, planning, inhibition, organizing and the ability to plan sequences [8].

Psycho-motor agitation and *aggressiveness* are seen right from the early stages of recovery and can damage the health of the patient and of his/her caregivers [9]. They are characterized by low tolerance of frustration and explosive behaviour set off by the slightest provocation and often without warning [10]. The aggressiveness can be verbal or even physical with the risk of damage for objects or people.

Systematic research in trials on pharmacological efficacy, carried out within the setting of neurobehavioural sequelae as defined above, has provided a scene of light and shade for advances in research on rehabilitation [3].

First of all, there is no evidence reaching the level of a Standard for any one of the three categories of neurobehavioural problems, a fact that highlights the chronic lack of studies in this field.

Nor is there evidence that reaches the level of *Guidelines* for psychiatric disturbances; however, the following guidelines are present for

(a) the pharmacological treatment of cognitive disturbances:
   1. phenytoin causes damage to the general cognitive functions, and should not, therefore, be administered;
   2. methylphenidate (0.25–0.30 mg kg^{-1} twice daily) is recommended for increasing the attention function, speeding-up cognitive processes and increasing sustained attention;
   3. donepezil (5–10 mg day^{-1}) is recommended for improving attention and memory in the sub-acute or chronic stages of recovery;
   4. bromocriptine (2.5 mg) is recommended for improving some aspects of executive functioning; and

(b) the pharmacological management of aggressiveness:
   1. β-blockers (propranolol 420–52 mg day^{-1}; pindolol 40–100 mg day^{-1}) are effective in the treatment of aggressiveness following brain trauma.

The following recommendations are, instead, to be considered as treatment options:

- use of tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI), Benzodiazepine, atypical antipsychotics for apathy, anxiety and psychosis;
- use of stimulants (methylphenidate), prodopaminergics (amantadine) for the improvement of cognitive functions in general;
- use of stimulants (destromethorphane), prodopaminergics (amantadine), cholinesterase inhibitors (physostigmine) for the improvement of attention and speed of elaboration;
- use of stimulants (methylphenidate) and CDP choline for the improvement of memory;
- use of stimulants (methylphenidate), cranial electrical stimulus, Homeopathy, SSRI (sertraline and paroxetine), antiepileptics (valproate), antimaniacals (lithium), antidepressants (amitriptyline, desipramine, buspirone) to control aggressivity.

The publication of these recommendations certainly represents a positive starting point for a body of doctrine under construction, and demonstrates that studies of good methodological quality are being produced. However, at the same time it confirms that there are substantial gaps concerning therapeutic questions commonly seen in rehabilitation clinical practice.

Despite this, the publication is still a positive contribution, which allows rationalization of a rather fragmented subject, and is of great clinical relevance. The guidelines quoted are unsatisfactory for at least two reasons:

1. the therapeutic efficacy of the pharmacological intervention is evaluated on the basis of resolving single symptoms without placing the intervention into the more complex context of the neurological recovery of the individual;
2. the possibility that the effective elimination of a symptom coincides with an 'inhibition' or a 'slow-down' of the neurobiological recovery (negative effect on neuronal plasticity) is not taken into consideration.

Treating a neuropsychological symptom pharmacalogically: how objectives change according to the context

Current clinical rehabilitation practice is carried out by interdisciplinary workgroups (doctor, nurse, physiotherapist, logopedist, psychologist) and the solution to single problems is set inside a global therapeutic rehabilitation project, which considers the person as a whole, from different points of view. The core of the rehabilitation project is represented

by a general strategy, which has the objective of speeding up the neurobiological recovery process of the patient. It is constituted by programmes adopted by single professionals who, though acting as single units, must act coherently with the general project.

To better clarify the dynamics that are generated between the rehabilitation project and the single programmes, a plausible example of clinical discussion as could occur within a neuro-rehabilitation team is given below.

'The patient is agitated, aggressive; the nurses are worried because he/she refuses the therapy and inadvisedly tries to get out of bed risking accidental falls; according to the doctor the most effective therapy is a neuroleptic which is administered and within a few days the patient is effectively sedated:

Thus sedated, the patient no longer collaborates with the therapist who complains to the team, and considers the effect of the drug negative, since he/she notes less psychomotor initiative and less collaboration in active motor treatment.

According to the nurses it is better to have the patient sedated and quiet in bed.

According to the therapist it is better to have the patient active, collaborative and motor efficient.

On the basis of these points of view it is necessary to make a choice which guarantees efficient sedation without negative effects on motor ability.'

As one notes in the example, the team is looking for an effective drug for sedation, which does not have undesired effects on the neuromotor, cognition or psychomotor sides. This need is confirmed by a statement already pointed out in the literature, according to which individuals with TBI are refractory to treatment with the usual psychotropic drugs, in that they are not responsive and more easily subject to undesired effects [11]. That is, many clinicians have the impression that some drugs in common use are not efficient or are associated with excessive toxicity in traumatized patients, and this is reported mainly for psychiatric types of drugs. The guidelines we previously referred to dedicate a specific section to this aspect and conclude that there is no reason to believe that cranial trauma patients are less responsive to psychotropic drugs and that the full range of undesired effects observed in the general population can also be found in TBI patients [3].

If the question is posed in terms of 'prevalence' this conclusion could be completely acceptable. However, if it is posed in terms of 'how much the undesired effect weighs' on the neurological recovery of a patient who also has a cognitive and/or motor deficit, then it could be worth making substantial revisions to the published conclusions.

It is one thing to provoke iatrogenic parkinsonism in a psychotic patient who is intact from a motor point of view and another to provoke it in a patient with a concomitant pyramidal or cerebral deficit: the impact on the independence of life is different.

The argument is not dissimilar from that used by the guidelines when they advise against the use of phenytoin in cranial trauma, in that it impedes the recovery of cognitive function in general. How many drugs have a negative effect on cognitive function? How many of these do we prescribe for cranial trauma patients? How many antiepileptics, neuroleptics, anxiolytics or antidepressants negatively influence the cognitive function of a patient already affected by a constellation of cognitive deficits provoked by trauma lesions? What has been demonstrated for phenytoin may also be suspected for a number of other sedating drugs, even though, to date, there are no experimental demonstrations.

We know the damaging effects of these drugs on cognitive function, thanks to the clinical information gathered on other patient populations, for example, the elderly.

It is known that among the elderly the long-term use of benzodiazepine increases the incidence of confusional postoperatory states [12] and represents an increased risk factor for cognitive decline [13]. The negative effect of the administration of benzodiazepine on the cognitive function has also been shown on healthy adults, in terms of a reduction of visuo-spatial ability and sustained attention [14,15], as well as meta-mnemonic ability, which is an accurate memory perspective, a function that requires participation and awareness [16]. A meta-analysis has calculated a moderate to large negative effect on all the cognitive domains when comparing long-term benzodiazepine users and controls [17].

The effect of neuroleptics on cognitive function is difficult to evaluate, but this field also has available indirect information on the negative effects.

A short period of administration of neuroleptics to healthy subjects has shown, in comparison to placebo, the appearance of disturbances of psychomotor functions and of verbal memory in association with atypical neuroleptics (olanzapine) and not with haloperidol [18]. A meta-analysis, however, clarifies that the negative effect of the haloperidol is dose dependent [19] and only appears at high doses (>10 mg), with the deleterious effects for doses higher than 24 mg. The condition of patients with schizophrenia is different, since during a psychotic attack they show notably diminished cognitive functions: in these patients the administration of atypical neuroleptics has shown cognitive improvement [20], better than that seen with atypical neuroleptics, even though at low

doses of haloperidol; such a difference in benefit is minimal [21].

Summing up, it is known that the administration of psychotropic drugs provokes undesired negative effects both on the motor side and on the cognitive side, and this knowledge leads us to recommend a cautious attitude in administering drugs to cure aggressiveness or psychiatric disturbances in TBI patients. The choice of these molecules, besides, should always be associated with dose moderation without nearing drug dosages normally reached in healthy patients.

Is the prescribed drug favouring or inhibiting neurobiological recovery?

As already mentioned, the second aspect to take into consideration when prescribing a psychotropic drug concerns knowledge of the action of the drug on the neurobiological recovery, which, as is known, depends on the neuronal plasticity processes [22].

It is supposed that some drugs can influence such processes in a positive or negative way and biological evidence of such effects comes from studies carried out on animals. It has long been known that cranial trauma reduces cerebral concentrations of monoaminergic neurotransmitters [23] and clinicians have experienced, mostly found in anecdotal annotations, clear accelerations of neurological recovery from brain trauma on the administration of monoaminergic drugs [24,25].

The most interesting animal experiment studies on this theme were conducted on rats and cats treated with unilateral ablations of the motor-sensorial cortex, in which the administration of D-amphetamine combined with motor-sensorial exercise produced an acceleration of recovery measured by walking on a beam [26,27].

According to the author the experiment increases, in a stable way, the speed of recovery of a neuromotor ability, which the cat is able to reacquire spontaneously over a longer period, and the administration of the neurotransmitter drug associated with motor-sensorial exercise acts as a catalyst in the process of neurological recovery.

The studies carried out have clarified extremely interesting aspects of this phenomenon, especially that the drug alone does not have the same positive effect as when administered together with motor-sensorial exercise; this was demonstrated by impeding the animal from physical exercise through opportune body restriction [26,28]. Once the experiment was completed, the recovered neuromotor ability remained stable over time, confirming that is was not a cosmetic effect, but a real neuromotor recovery; in contrast to the recorded positive effects on recovery through the work of neurotransmitter drugs, negative effects of the action of their natural antagonists demonstrate that the administration of some drugs may even have a negative function [27,29].

Studies carried out with pure receptor *antagonists* have shown that the stimulation of the α_1-NA receptors is a central element of this positive effect on the functional recovery after cortical lesions [27] and that:

1. the central antagonists of the α_1-adrenergic receptors inhibit motor recovery (prazosine and phenoxybenzamine);
2. the antagonists of the α_2-adrenergic receptors, acting at a central level, increase the release of norepinefrine and favour motor recovery (ioimbine and idazoxan);
3. the α_2-adrenergic agonists have an inhibitory effect (clondine);
4. the antagonists of the α_2-adrenergic receptors have no negative effect on the motor recovery (β-blockers);
5. haloperidol produces a negative effect, it being a dopaminergic antagonist and also a noradrenergic antagonist.

Reading the data from animal experimentation must be carried out with caution, especially when the intention is to derive information to translate to human clinical experience.

What is sure, though, is that while the certainty of the effect of a single drug is not predictable, it is possible to set up a conceptual scheme to analyse the potential benefit or damage of a group of neurotransmitter drugs, and on the basis of this scheme, to compare the therapeutic choices for single symptoms: classifying macrocategories of drugs on the basis of a potential effect favouring or inhibiting neurobiological recovery.

Although there is no certainty about their positive effect, the suspicion that commonly used drugs, such as clondine used for antihypertension, or haloperidol prescribed for controlling psycho-motor agitation, inhibit recovery has led to a continuous effort to find alternatives for every symptomatic therapeutic choice.

Efficiency studies, which do not have the disappearance of some symptom as their end goal but evaluate the results according to a global vision of recovery that only the interdisciplinary approach provides are indispensable.

1. Objective: inhibit the symptom
   Outcome: 'disappearance of the symptom';
2. Objective: inhibit the symptom without producing negative effects on the rehabilitation project

Outcomes: 'disappearance of the symptom' and 'no negative effect on the rehabilitation project';
3. Objective: inhibit the symptom without producing negative effects on the rehabilitation project and without inhibiting neurological recovery
Outcomes: 'disappearance of the symptom' and 'no negative effect on the rehabilitation project', 'speeding-up//enhancing the neurological recovery'.

In the third scheme the speeding-up of the recovery is the primary outcome, while the disappearance of the symptom represents a secondary outcome.

Conclusions

Pharmacological intervention in rehabilitation has increasingly become the object of studies on effectiveness and, over the last few years, has shown progressive improvement in their methodological quality.

Guidelines have been published that have ordered the scientific evidence available to date and allowed for the rationalization of the theme of neurobehavioural sequelae following severe TBI.

Studies on effectiveness, which take into consideration not only the resolution of the symptoms but also the influence of the drug on the rehabilitation project and above all on the neurobiological recovery process, are necessary.

We require rules for prescribing, which respect the following needs:

- the therapeutic choice must not be self-referring (according to the doctor's point of view);
- correction of the symptoms must be considered in relation to the project as a whole, harmonizing different points of view (interdisciplinary vision of a pharmacological strategy);
- in prescribing any drug, one must take into consideration the hypothesis that it may favour or damage the patient's neurobiological recovery (primary outcome of the rehabilitation project).

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