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Should we care about sativex-induced neurobehavioral effects? A 6-month follow-up study

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Abstract. – OBJECTIVE: Sativex® is an exclusive cannabinoid-based drug approved for the treatment of spasticity due to Multiple Sclerosis (MS). The most common side effects include dizziness, nausea, and somnolence. However, it is still under debate whether the drug could cause negative cognitive effects. The aim of our study was to investigate the effect of Sativex® on functional and psychological status in cannabis-naïve MS patients.

PATIENTS AND METHODS: All the study participants (i.e. 40 patients affected by MS) underwent a specific clinical and neuropsychological assessment to investigate spasticity and associated symptoms, besides the cognitive and psychiatric domains commonly impaired in MS, before and after 1 and 6 months of Sativex® administration.

RESULTS: After the treatment, we did not observe any significant neurobehavioral impairment in all the patients, but one.

CONCLUSIONS: Our findings suggest that Sativex® treatment does not significantly affect the cognitive and neurobehavioral functions. However, the study supports the relevance of an extensive neuropsychological evaluation in MS patients selected for the drug administration, in an attempt to early detect the uncommon but important neurobehavioral side effects.

Key Words:
Multiple sclerosis, Behavioral side effects, Cannabinoids, Sativex.

Introduction

The endocannabinoid system is considered to be involved in the pathophysiology of multiple sclerosis (MS), since self-medicating MS-patients report pain and spasticity relief after marijuana intake. Growing evidence is showing that cannabis may have adverse effects on cognition, attention[1,2], working memory[3], verbal learning, memory[4], and executive functions[5,6]. Moreover, cannabis use may cause neurobehavioral alterations, leading to a higher risk of major depression[7] and suicide[8]. On the other side, some studies did not report a significant correlation between cannabis use and cognitive impairment[9,10].

Δ-9-tetrahydrocannbinol (THC), the main psychoactive cannabis compound, may be the responsible for cognitive and psychiatric effects, including anxiety, depression[11,12], and schizophrenia[13], and this has been reported to worsen the course of neuropsychiatric diseases in cannabis users. Cannabidiol (CBD) has THC-opposite properties, i.e. anxiolytic[14] and antipsychotic[15], and it does not seem to cause cognitive deficits[16].

Sativex® is a unique cannabinoid-based drug containing 1:1 mixture of THC and CBD, approved in some countries, including Italy, for the treatment of MS-associated spasticity and the correlated symptoms (including spasms, pain, and mobility restrictions) that can interfere with quality of life (QoL).

It is still under debate whether these components could cause negative cognitive and neurobehavioral effects. Indeed, there is some evidence that CBD and THC co-administration may reduce the THC psychotropic effects, since CBD has THC-receptor modulation and neuroprotective properties[17]. Psychotic symptoms have been rarely reported during Sativex® therapy, so far[18,19]. Indeed, Robson et al[20] noted that only 3% of their patients developed euphoria and depression during treatment, with nobody showing cannabis withdrawal syndrome. On the contrary, the CAMSPEC study has demonstrated that MS patients treated with oral-THC presented with a significant increase in verbal learning impairment[21]. However, a review by Papathanasopou-

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los et al[22] concluded that cannabinoid therapy does not cause significant alterations in cognitive functions.

Aims of our study were: i) characterizing the effects of 1- and 6-month Sativex administration in cannabis-naïve MS patients on their neurobehavioral function; ii) evaluating the drug tolerability and possible abuse phenomena induction; and iii) studying the effects of cannabis on QoL and motor functions, using a specific clinical and neuropsychological assessment.

Patients and Methods

Patients

We consecutively enrolled 61 MS patients (whose diagnosis was reached according to the revised McDonald criteria)[23] that attended the MS Center of IRCCS in Messina (Italy) between January and December 2014. As primary inclusion criterion, the patients had to present with moderate-to-severe spasticity due to MS (numerical rating scale for spasticity NRS ≥4) with evidence of inadequate response to the traditional anti-spastic medications (thus, all the patients had to be in treatment with Sativex®). In addition, patients had to match the following secondary inclusion criteria: age > 18 years; a diagnosis of definite MS since at least six months; right-handed with normal right-hand function; a moderate to severe spasticity; the absence of clinical or neuroradiological relapses since at least six months; a baseline Expanded Disability Status Scale score (EDSS) ranging from 3.5 to 8; no changes in anti-spastic and immune-modulator agents (dosage, frequency, and route of administration) before their study enrollment; no history of psychiatric disorders, cardiovascular diseases or epilepsy (in agreement with the Italian Agency of Drug rules); no use of other cannabinoid-based medications (e.g. oral cannabinoid, smoked cannabis). The clinical characteristics of the patients are reported in Table I. All the subjects were taking antispastics, being baclofen the most commonly used; in addition, only 40% of patients were under pharmacological treatment for other reasons than spasticity.

Patients were informed about the potential Sativex® side effects (including the neurobehavioral ones), and they gave their written informed consent to be included into the study, which was approved by the local Ethics Committee.

Experimental Design

The 61 recruited patients underwent a neurological and neuropsychological examination. In addition, we assessed the mean reaction time (RT) to a simple hand motor task. Therefore, they were administered a first "drug titration period" (4 weeks), during which a progressive increase in Sativex® dosage was scheduled, according to a fixed scheme (Table II). Then, the patients showing a reduction in NRS ≥ 20% were classified as responders (45) and continued the drug intake in the "treatment phase" (up to 6 months). The other patients were considered as non-responders, and withdrew drug intake.

Table I. Demographic characteristics of the enrolled, responders and non-responders patients at baseline (T0). Notably, 19 out of 61 patients had a relapsing remitting (RR) course, reflecting the fact that spasticity is more frequent in the later phases of the disease.

	Whole sample (61)	Responders (45)	Non-responders (16)
Age (y)	42 ± 8.9	43 ± 9	42 ± 8
Disease duration (y)	9	9	10
Disease course	19 RR	14RR	5RR
	42 SP	31SP	11SP
Disease-modifying drugs	20 IFN	15 IFN	5 IFN
	5 GA	4 GA	1 GA
	8 NTZ	5NTZ	3 NTZ
	10 FTY	4 FTY	6 FTY
	18 no-treatment	17 no-treatment	
Symptomatic treatment	59 Baclofen	43 Baclofen	16 Baclofen
	2 Tizadine	2 Tizadine	

Legend: y year; RR relapsing-remitting; SP secondary-progressive; IFN interferon; GA glatiramer-acetate; NTZ Natalizumab; FTY fingolimod.

Study Drug

Patients received the cannabis-based drug (Sativex®, GW Pharma, UK) by means of a pump action sublingual spray. Sativex is composed of a cannabis plant extract, containing THC (27 mg/ml) and CBD (25 mg/ml), and ethanol/propylene glycol (50:50) excipient. Each actuation delivered 100 μL of spray, containing 2.7 mg of THC and 2.5 mg of CBD. The mean number of sprays administrated during the titration period is reported in Table II.

Clinical Assessment

All the patients underwent a complete neurological, neuropsychological, and RT examination at baseline (T_0), and after 1 (T_1) and 6-month (T_6) of Sativex® intake, including:

- The Expanded Disability Scale (EDDS) is aimed at creating an objective approach to quantify the level of functioning that could be widely used by health care providers diagnosing MS. It provides a total score ranging from zero to 10, in which the first levels (from 1 to 4.5) refer to people with a high degree of ambulatory ability, whereas the subsequent levels (5 to 9.5) refer to the loss of such function.
- The Modified Ashworth Scale (MAS), which is considered the primary clinical measure of muscle spasticity in patients with neurological disorders.
- The numerical rating scale (NRS), which is a patient-reported outcome measure that reliably assesses spasticity.
- The visual analogical scale (VAS) for chronic pain rating.

Table II. Titration schedule. The number of sprays was gradually augmented within 10 days up to 8-9 puffs (distributed during morning – from 8^{am} to 2^{pm} – and evening time – from 2^{pm} to 8^{pm}).

Day	Number of sprays		
	Morning	Evening	Total
1	0	1	1
2	0	1	1
3	0	2	2
4	0	2	2
5	1	2	3
6	1	3	4
7	1	4	5
8	2	4	6
9	2	5	7
10	3	5	8
11-30	4	5	9

The neuropsychological assessment consisted of a specific battery focusing on those cognitive domains commonly impaired in MS, including the Montreal Cognitive Assessment (MoCA), the attentive matrices (AM), the trial making test (TMT-A, B, BA), the Babcock Story Recall Test (BSRT), the Zung-Sas Scale (ZSS), and the Multiple Scleroses QoL (MSQoL-54) (see Table III).

Finally, we measured the RT during a simple hand motor task. RT is the elapsed time between the presentation of a go-signal and the subsequent behavioral response, which is considered as an index of processing efficiency concerning the executing mental operations needed by the hand-motor task[24]. Subjects were sitting in front of a monitor, with the right hand resting comfortably on a surface. They were asked to completely relax between the trials. During each trial, they were asked to briskly abduct the right thumb in response to a go signal presented on the screen, in order to produce a single electromyographic (EMG) burst. No prior warning signal was given. All the participants performed the task correctly after few minutes of training. The RT was defined as the interval between the go-signal and the onset of EMG burst. We assessed the mean RT considering twenty of these RT trials. EMG was recorded using a pair of Ag-AgCl surface electrodes placed over the abductor pollicis brevis using a belly-tendon montage. Raw signals were amplified and filtered at 20Hz-3kHz (Neurolog System, Digitimer Ltd., Welwyn Garden City, Herts, UK) and digitalized using a CED1401 laboratory interface (Cambridge Electronic Design Ltd., Cambridge, UK). Data were collected on a personal computer (Signal 3.0, Cambridge Electronic Design Ltd., Cambridge, UK) and analyzed off-line. High gain audio-visual EMG monitoring was used to ensure complete muscular relaxation.

Statistical Analysis

Comparison of baseline with post-treatment data was performed using the nonparametric Wilcoxon signed rank test to calculate the p-value. $p < 0.05$ was considered statistically significant.

Results

Sixteen out of the 61 enrolled patients were classified as non-responders to "drug titration period" and were thus excluded from the "treatment phase". Five out of these 45 patients discontinued the drug intake: one had adverse events (i.e. suici-

Table III. List of the tools used in psychological well-being assessment.

Montreal cognitive assessment (MoCA)

It assesses several cognitive domains:
- The short-term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately 5 minutes.
- Visuo-spatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point).
- Executive functions are assessed using an alternation task adapted from the trail-making B task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points).
- Attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each).
- Language is assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points), and the aforementioned fluency task. Finally, orientation to time and place are evaluated (6 points).

Attentive matrices (AM)

It investigates selective attention process. It is a test of barrage, which includes three different matrices of numbers (5-26-149); the patient must barrage the matrices in presence of distracters numbers during 45 second for each matrices.

Trial making test (TMT-A, -B, -B-A)

It is finalized to evaluate the visual-spatial attention, the attentive shifting and interaction between the working memory and the executive functions. This test is composed by two different sub-tests. In the first examination, the patient must associate the numbers from 1 to 25; in the second subtest, the subject associates in alternative sense one letter with a number in progressive order.

Zung-sas scale (ZSS)

It is a 20-item self-report assessment device builded to measure anxiety levels, based on scoring in 4 groups of manifestations: cognitive, autonomic, motor and central nervous system symptoms. The total raw scores range from 20 to 80. The raw score needs to be converted into an "Anxiety Index" score, using the chart on the paper version of the test. The “Anxiety Index” score can then be used on this scale below to determine the clinical interpretation of one’s level of anxiety: 20-44 normal range; 45-59 mild to moderate anxiety levels; 60-74 marked to severe anxiety levels; 75-80 extreme anxiety levels.

Babckock story recall test (BSRT)

It is a verbal memory measure in which participants are read a brief story and asked to provide.

Multiple sclerosis quality of life (MSQoL-54)

It combines both generic and MS-specific items into a single instrument. The developers utilized the SF-36 as the generic component to which 18 items were added to tap MS-specific issues such as fatigue, cognitive function, etc. This 54-item instrument generates 12 subscales along with two summary scores, and two additional single-item measures.

dal ideation)[19] and 4 were lost at follow-up. After one and six months of Sativex® intake, the main reported side effects were dizziness, dry mouth, nausea, and mild generalized weakness. No significant changes were observed at blood tests. Moreover, blood pressure, weight and body temperature (that were daily measured by the patients or their caregivers) were unchanged.

The patients showed a significant NRS and MAS decrease (Table IV). Notably, neither the neuropsychological nor the RT performances were significantly affected by Sativex administration, although we observed a mild ZSS increase (Table IV).

Discussion

Neurobehavioral alterations affect up to 65% of MS patients, with negative consequences on personal, social, and occupational performances[25]. The impairment in the cognitive domains, including memory, mental processing speed, attention, and executive function, can occur also in the early stage of the disease, and tends to worsen over time, resulting in significant functional impairment, despite the presence of minimal physical disability[26-28]. It is well known that THC can induce psychotic symptoms and anxiety, and impair memory[11] and psychomotor

Table IV. Neuropsychological results of the "responder patients". Data are reported as mean ± SD or mean (range). The statistically significant changes at T1 and T6 in comparison to baseline values (T0) are superscripted.

Parameters		T0 (45)	T1 (45)	T6 (40)
MoCA		28 ± 1	28 ± 1	28 ± 1
TMT	A	79 ± 6	74 ± 7	72 ± 6
	B	181 ± 18	168 ± 19	166 ± 19
	B-A	115 ± 16	94 ± 13	93 ± 14
AM		42 ± 1	43 ± 1	43 ± 1
BSRT		8 ± 1	9 ± 1	9 ± 1
ZSS		32 ± 1	33 ± 1	35 ± 10.02
MSQoL-54	Physical	55 ± 2	49 ± 2	55 ± 2
	Mental	66 ± 4	66 ± 2	72 ± 4
NRS		8 (7-10)	5 (2-7) < 0.001	5 (2-7) < 0.001
EDSS		7 (2-9)	6 (2-9)	6 (2-9)
MAS		4 (2-4)	3 (2-4) 0.002	2.9 (1-3) < 0.001
RT		195 ± 36	209 ± 33	201 ± 34

Legend: MoCA Montreal Cognitive Assessment; AM Attentive Matrices; TMT Trial Making Test; ZSS Zung-Sas Scale; BSRT Babckock Story Recall Test; MSQoL-54 Multiple Sclerosis Quality Of Life; NRS numerical rating scale; EDSS expanded disability status scale; MAS modified Ashwort scale; RT reaction time.

control in healthy individuals[29]. In addition, the regular THC consumption is thought to exacerbate psychiatric symptoms and increase the risk of developing schizophrenia[30]. The abundance of cannabinoid receptors in the hippocampus, amygdala, basal ganglia, and prefrontal cortex[31] may suggest that the dysregulation of the cannabinergic system by administration of exogenous cannabinoids, including THC, could affect several neurobehavioral processes, such as mood and anxiety regulation[32], learning, memory, motivation, motor control, reward processing, and executive functions[33]. Thus, the potential impact of cannabinoids on cognitive functions in MS needs to be carefully evaluated.

Our findings suggest that Sativex® do not significantly affect cognition when used at the mean therapeutic dosage (i.e. 8-9 daily puffs), since we did not observe any significant modification concerning visual-spatial attention, attentive shifting, calculation, language, ability to follow simple commands, orientation, memory, and executive functions. Notably, these results were corroborated by the fact that also RT (an objective neurophysiological measure of attention) remained unchanged after the drug treatment.

In our sample, we only noted a mild increase in anxiety (as per ZSS scoring). Previous studies have shown that Sativex® has not significant detrimental effects on cognition or mood, and that it does not affect driving ability[34,35]. Markedly, Aragona et al[36] found a positive correlation between THC blood levels and abnormal scores at psychological tests, suggesting that individual sensitivity, aggressiveness, and paranoid features might arise at dosages higher than those used in therapeutic settings.

Since CBD has neuroprotective[37], anxiolytic, and antipsychotic properties[38], and it does not impair memory or other cognitive functions[16,39], the combination of THC and CBD in equivalent doses could be the reason why, in our patients, we found an extremely low rate of neurobehavioral side effects, and a lack of neuropsychological harmful effects.

Notably, after a month of Sativex® administration, we observed psychotic symptom onset (including suicidal ideation) in one patient, who was using a relatively high daily drug dosage (12 *vs*. 9 puffs), had a baseline ZSS score of 47, and was treated with other psychoactive drugs[19]. Indeed, these symptoms disappeared after 10 days of drug withdrawal. Thus, it is hypothesizable that Sativex® could cause psychiatric effects in predisposed individuals, since growing evidence is suggesting that the overlap of the genetic contributions to depressive disorder with specific additional events (as a new drug introduction) could precipitate the depressive illness[40].

Conclusions

Our findings show that Sativex treatment does not significantly affect the cognitive and neurobehavioral domains at a moderate dosage.

However, the study supports the relevance of an extensive neuropsychological evaluation in patients who are selected for the drug administration, in an attempt to early detect the uncommon but important neurobehavioral side effects.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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