Efficacy and safety of a GABAergic drug (Gamalate® B6): effects on behavior and cognition in young adults with borderline-to-mild intellectual developmental disabilities and ADHD

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Abstract

Background: We evaluated Gamalate® B6 (GB6) in patients with borderline intellectual functioning (BIF) or mild intellectual development disability (IDD).

Patients and methods: This was a prospective phase IV observational pilot study in 30 patients who underwent neuropsychological evaluation during treatment with GB6 for 12 weeks.

Results: In comparison with baseline, the responses were positive, with a significant improvement in hyperactivity (51.7%), irritability (35.5%), and logorrhea (50%), and no sedative effect. The Clinical Global Impressions – Severity (CGI-S) score was much improved or very much improved in 73% of cases. Reaction time was better with fewer errors, thus indicating an improvement in attentional processes. A statistically significant result was obtained for the number of movements used to solve the problem and for the total number of correctly solved problems.

Conclusion: In this pilot study, GB6 was effective and well tolerated in cases of ADHD and challenging behavior in young adults with borderline-to-mild BIF/IDD. However, given the small number of patients involved and the uncontrolled nature of the study, these results should be viewed cautiously.

Keywords: attention-deficit hyperactivity disorder, challenging behavior, young adults, GABAergic system, Gamalate B6.

Citation

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Introduction

Challenging behavior is the nonspecific expression of neurobiological, psychological, and socioenvironmental factors and may manifest as aggression, noncompliance, and hyperactivity. It is also the main reason for psychiatric consultation and psychopharmacological treatment in people with intellectual development disabilities (IDD). Regardless of the cognitive level, 30–40% of people with IDD present challenging behavior.1–4

Although pharmacological treatment should not be considered the first and only approach in people with IDD and challenging behavior, drugs that act on the central nervous system (CNS), such as antipsychotics, have been considered as an effective way to control the challenging behavior in this population.5,6 Moreover, many antipsychotics have short- and long-term adverse effects8–16 and are therefore contraindicated in specific cases, mainly in vulnerable populations.

Challenging behavior is shared by various neurodevelopmental disorders, such as attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and IDD/borderline intellectual functioning (BIF). ADHD is a common childhood behavioral disorder. Symptoms start in early childhood and continue into adulthood. Systematic reviews indicate that community prevalence is between 2% and 7% in adults, with an average of around 5%. At least a further 5% of children have substantial difficulties in the form of overactivity, inattention, and impulsivity that almost meet the full diagnostic criteria for ADHD.17,18 Adult ADHD symptoms may not be as clear as ADHD symptoms in children. In adults, hyperactivity may decrease, although...
struggles with impulsiveness, restlessness, and difficulty paying attention may continue and can lead to problems such as unstable relationships, poor work or school performance, and low self-esteem. Treatment of ADHD includes amphetamine derivatives such as methylphenidate, which are increasingly prescribed worldwide in children and adults. However, it is noteworthy that 70% of treated cases do not meet the diagnostic criteria for ADHD. In addition, the consumption of anxiolytics and hypnotics in Europe is increasing, and approximately 13% of patients with intellectual disability experience the behavioral adverse effects of benzodiazipine. The four most frequently reported behavioral side effects are aggression, irritability, hyperactivity, and agitation.

Interest in γ-amino-butyric acid (GABA) enhancers for treatment of behavioral and cognitive disorders in people with IDD and BIF stems from their hypothesized role in psychiatric and neurological disorders such as anxiety, stress, post-traumatic stress disorder, depression, ADHD, autism, epilepsy, insomnia, and movement disorders such as Tourette’s syndrome, Parkinson’s disease, and tardive dyskinesia. GABA plays a functional role in establishing and refining neuronal circuits early in postnatal development and in the molecular mechanisms that regulate the excitatory/inhibitory balance. A dysfunction of GABAergic signaling early in development leads to a severe excitatory/inhibitory imbalance in neuronal circuits, which may account for some of the behavioral deficits observed in neurodevelopmental disorders.

Anxiety, a key behavior in ASD, is probably associated with the altered excitatory/inhibitory balance. A synaptic hyperactivation with low GABAergic activity and amygdala hyperconnectivity with pronounced activity of noradrenaline and glutamate has been proposed in ASD. To date, the evidence has been fairly indirect although a new study links symptoms of autism to reduced GABA activity. The authors used magnetic resonance spectroscopy to measure GABA levels in 17 adolescents and young adults with autism and 20 age-matched control participants. The researchers believe their results point to potential treatments for autism in the form of drugs that might increase GABA concentrations.

Recent evidence suggests that there is a deficit in cortical inhibition via the GABAergic system and that the mean GABA concentrations are significantly lower in ADHD patients than in normally developing control subjects. Cerebral cortical inhibitory function via GABAergic transmission may be crucial for filtering sensory information and selecting appropriate behavioral responses. Increased GABA transmission in the prefrontal regions may be the neural basis underlying improvement in social competence.

An effective intervention for many hyperactive children, besides methylphenidate and other psychostimulants, is the use of vitamin B6 (pyridoxine) and magnesium (Mg). Magnesium acts mainly by inhibiting the glutamate N-methyl-aspartate channel, which is associated with an influx of calcium and, in turn, excitotoxic cell death and apoptosis. Therefore, while Mg has been shown to be a nonspecific calcium channel inhibitor, it could act as an N-methyl-D-aspartate channel inhibitor. Similarly, Mg could influence catecholamine signaling in the brain. Intraerythrocytic Mg depletion has been observed in ADHD patients, and increased hyperactivity and decreased attention at school were associated with decreases in Erc-Mg values. This observation was supported by the fact that Mg-B6 supplementation induced a rise in Erc-Mag values and a concomitant improvement in clinical symptoms.

Gamalate® B6 (GB6) is formulated as a coated tablet containing: magnesium glutamate hydrobromide (MGHB) 75 mg, GABA 75 mg, γ-aminobutyric acid (GABOB) 37 mg, and pyridoxine hydrochloride (vitamin B6) 37 mg. It has played a role in recovery in nervous system disorders that occur with nervous hyperexcitability or metabolic deficits and has proven to be effective and safe.

Treatment with GB6 has proven effective in fibromyalgia by reducing pain and fatigue. It also improves symptoms of anxiety and tension headache accompanied by anxiety or depression by inducing a euthymic effect. Numerous studies have demonstrated the efficacy of GB6 on the intellectual performance of children with and without intellectual disabilities. In a previous study in children with mild-to-moderate IDD, the authors suggested that GB6 could be an effective and safe treatment for behavioral disorders, mainly hyperactivity and agitation. At the end of a 3-month treatment period, a statistically significant reduction was observed in the mean score obtained in all subscales of the Aberrant Behavior Checklist (ABC).

The main purpose of this study was to evaluate the effectiveness and safety of 12 weeks of treatment with GB6 on adaptive skills and behavioral and cognitive performance in young adults with BIF/IDD with or without ASD who have been clinically diagnosed with ADHD and challenging behavior.

**Patients and methods**

**Study design**

This was a single-centered, prospective, phase IV, observational pilot study in 30 participants with borderline-to-mild intellectual developmental disabilities and ADHD who were treated with GB6 for 12 weeks using the approved dosage included in the package insert and who underwent neuropsychological assessment.

**Participants**

Patients were included using non-probabilistic convenience sampling among the outpatients of the Specialized Service in Mental Health and Intellectual Disability (SESM-DI) and who met...
the inclusion criteria. Candidates underwent a comprehensive neuropsychological evaluation, as well as an adaptive and behavioral study. To be included in the study, patients had to be aged between 16 and 25 years with a diagnosis of BIF or IDD and ADHD according to DSM-V criteria. They also had to present challenging behavior. ASD was diagnosed based on the Autism Diagnostic Observation Schedule (ADOS) test, a semi-structured, standardized assessment of social interaction, communication, play, and imaginative use of materials, which consists of four 30-minute modules, each designed to be administered to different individuals according to their level of expressive language.

Patients also had to have a relative or guardian to legally represent them and sign the informed consent if they were unable to do so.

The exclusion criteria were as follows: moderate or severe IDD, previous CNS abnormalities not related to IDD (e.g. head injury, cerebrovascular accident, brain tumor, multiple sclerosis), substance abuse, presence of associated untreated diseases (hypothyroidism, vitamin B12 deficiency, diabetes mellitus), cognitive deficit, severe sensory limitations that prevented adequate assessments, absence of informed consent, and known allergy to the components of GB6.

This study was carried out according to the International Ethical Guidelines for Epidemiological Studies (CIOMS, Geneve, 2009), the Declaration of Helsinki (AMM, Seoul, October 2008), and Law 14/2007 on Biomedical Research published in the Spanish Official Gazette. Institutional review board approval was obtained from Parc Hospitalàri Martí i Julià, Girona, Spain on 20 December 2016 and written informed consent was obtained from the participants or relatives/guardians.

### Procedures and clinical assessments

Each participant underwent a comprehensive behavioral and neuropsychological evaluation at baseline and during treatment (Table 1). For the primary outcome measures, the evaluation included the ABC, which was used to assess emotional and behavioral symptoms on the hyperactivity subscale (e.g. excessive activity, impulsivity, inability to remain calm, disobedience, does not pay attention, is easily distracted), irritability (e.g. aggression toward others, deliberate self-injury, temper tantrums), as well as the other ABC subscales, such as stereotypy, logorrhea, and lethargy. The CGI-S scale was also used. Clinically significant behavioral problems were defined as a score of ≥13 on the hyperactivity/irritability subscales of the ABC and by a rating of moderate or higher on the CGI-S scale, as determined by a clinician. A positive response to treatment was defined as a ≥25% improvement in the score on the hyperactivity/irritability subscale and a rating of much improved or very much improved result on the CGI-S scale. We also used the Adaptive Behavior Assessment System, Second Edition (ABAS-II), which is a behavior rating scale typically completed by a caregiver to study 10 adaptive skills and 3 conceptual domains (self-care, self-direction, and social interaction). Its objective is to provide a complete evaluation of a person’s functional abilities to determine whether they are able to function in their daily lives without the support of other people.

### Specific neuropsychological testing

#### Intellectual quotient

We applied the Kaufman Brief Intelligence Test, Second Edition (K-BIT-2), using only the Matrices subtest as a nonverbal subtest. The test is widely utilized for research in people with IDD because it gives a standard base score of 40. The test was applied just once.

#### Attention

The Conners Kiddie Continuous Performance Test, Second Edition (K-CPT 2) comprises measures of inattention, impulsivity, sustained attention, and alertness. The patient is asked to respond to the targets (all objects except the football) and to refrain from responding to the nontargets (the football) that appear on the computer screen. The Color Trail Test (CTT1 and CTT2) was used to evaluate sustained attention as well as processing speed, shared attention, and mental flexibility.

### Table 1. Test used to evaluate behavior, adaptive, and cognitive skills.

| Test                                      |
|-------------------------------------------|
| **GENERAL INTELLIGENCE**                  |
| • Kaufman Brief Intelligence Test II      |
| **BEHAVIOR**                              |
| • Aberrant Behavior Checklist (ABC)       |
| • Adaptive Behavior Assessment System, Second Edition (ABAS-II) |
| • Clinical Global Impression – Severity (CGI-S) |
| **ATTENTION ABILITIES**                    |
| • Conners Kiddie Continuous Performance Test, Second Edition (K-CPT 2) |
| • The Color Trail Test                     |
| • Digits Forward WAIS-III series           |
| **MEMORY ABILITIES**                       |
| • Repeatable Battery for the Assessment of Neuropsychological Status (R-BANS) |
| **PSYCHOMOTOR SPEED AND MANUAL DEXTERITY** |
| • Purdue Pegboard Test                     |
| **EXECUTIVE FUNCTIONS**                   |
| • TOL-Dx                                   |
| • BRIEF-P                                  |
| **AUTISM DIAGNOSIS**                      |
| • Autism Diagnostic Observational Schedule (ADOS) |
We also applied the Memory for Digit Span assessment (Digits Forward), a component of the Wechsler Intelligence for Adults (WAIS IV), to study sustained attention and short-term auditory information.

**Memory**
Memory was assessed using a version of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) adapted for people with ID. There are four different memory versions to avoid a possible learning effect. This test evaluates different cognitive domains. We assessed learning, free delayed recall, and verbal recognition. Participants were read a list of 10 words and were asked to repeat as many words as they could remember. The same list was repeated over four trials. After 20 minutes, they had to recall information and then the recognition process.

**Psychomotor speed and manual dexterity**
The authors assessed these items using the Purdue Pegboard Test, which measures two elements of manual dexterity. It is used to detect laterality of brain damage, identify patients with learning difficulties, and measure the performance of patients with neurological-based learning difficulties.

**Executive processes**
A version of the Tower of London-Drexel University, Second Edition (TOLDXem) for persons with IDD was used. The planning sequence begins with an objective, mentally rehearsing, applying one’s chosen strategy, and finally appraising whether or not the objective is achieved. The Behavior Rating Inventory of Executive Function (BRIEF) was also administered. In this case, we managed the parent form, called BRIEF-Parents (BRIEF-P). This interview evaluates eight domains of executive function: inhibit, shift, emotional control, initiate, working memory, plan/organize, organization of materials, and monitor.

Efficacy ratings were collected monthly by two masked raters: a psychiatrist specialized in IDD, who monitored efficacy and measured adverse events, and a trained neuropsychologist, who evaluated cognitive function and adaptive skills (Table 1). Patients were seen monthly during the 12 weeks of the study. At the first visit, the psychiatrist collected the clinical history and sociodemographic data of each participant and the neuropsychologist administered the cognitive protocol (cognitive exploration and questionnaires to the family members). Patients received GB6 at a dose of six coated tablets a day distributed in three intakes (MGHB 450 mg/day, GABA 450 mg/day, GABOB 225 mg/day, B6 225 mg/day). At the second and third visits, the neuropsychological assessment protocol was applied. At the last session, participants and relatives were informed of the individual results for each case. The assessment sessions lasted 1 hour, except the first one, which lasted 3 hours.

### Safety monitoring
All adverse effects were recorded, together with their causal relationship, severity, and consequences. Adverse events not related to the treatment were also recorded.

### Statistical analysis
As an intrasubject design was used, the effect of the demographic and clinical variables of the participants remained constant in the pre- and post-measurements, thus reducing error variance. Therefore, a sample of 30 participants was considered sufficiently large to find clinically relevant differences in the different efficacy measures of GB6.

A descriptive analysis of all the study variables was carried out using measures of central tendency and dispersion for the continuous quantitative variables and frequencies and percentages for the categorical variables. The effectiveness of GB6 in the different behavioral measures and cognitive performance was analyzed by comparing pre and post means with t-tests for dependent measures, in the case of normally distributed variables. The Wilcoxon test was used for nonnormally distributed variables.

A randomized audit process was carried out in between 10% and 15% of the patients included on in the case report form to guarantee confidentiality.

### Results
The mean age of the 30 patients included was 20.25 years (16.00–24.50). The mean IQ was 77, with an interval of 67±2.3 for mild IDD and 88±1.8 for BIF. A total of 12 participants (40%) had ASD (Table 2).

### Primary outcome
At the end of the treatment period, the main score obtained in most of the subscales of the ABC Scale had decreased significantly. The maximum reduction was obtained in the subscale evaluating hyperactivity, which decreased from 14.5
The main results obtained with the Conners K-CPT 2 after the first month of treatment were as follows: (1) better discrimination between targets and nontargets (detectability), which decreased 13 points from 64.00 (IQR, 46.00–76.00) [L0] to 51.00 (IQR, 45.00–65.00; p=0.014) [L1], thus indicating better attentiveness; (2) fewer incorrect responses to nontargets (commission errors), which decreased 9 points from 52.00 (IQR, 41.00–72.00) [L0] to 41 (IQR, 38.00–57.00; p=0.021) [L1], thus indicating a decrease in inattentiveness or impulsivity; (3) less perseverance, which decreased 2 points from 50.00 (IQR, 48.00–78.00) [L0] to 48.00 (IQR, 46.00–60.00; p=0.019) [L1], thus indicating decreased impulsivity; (4) improved consistency of speed response (HRT SD), which decreased 13 points from 63.00 (IQR, 47.00–77.00) [L0] to 50.00 (IQR, 43.00–75.00; p=0.036) [L1], thus indicating improved attentiveness (Table 5). The results for Digit Span revealed an improvement in the effectiveness of sustained attention, thus indicating better attention skills, which increased in the following months. There was an improvement in Span (numbers that the patient is able to repeat) from 3.00 (IQR, 2.75–4.00) [L0] to 4.00 (IQR, 3.00–5.00; p=0.012) [L1] during the first month of treatment and to 4.50 (IQR, 3.75–5.25; p<0.01) [L2], and by 7.5 points to 7.00 (IQR, 4.00–12.50) [L0] to 12.5 (IQR, 3.50–25.50; p>0.01) [L1], and by 7.5 points to 7.00 (IQR, 3.00–16.50; p=0.063) [L2]. Irritability declined from 15.50 (IQR 4.00–25.25) [L0] to 13.50 (IQR, 7.00–27.50; p>0.01)1[L1] and by 5.5 points to 10.00 (IQR, 4.50–26.50; p<0.05) [L2], as did stereotypy by 2 points from 4.50 (IQR, 1.50–7.75) [L0] to 2.50 (IQR 0.75–6.25; p=0.025) [L1]. Logorrhea decreased from 4.00 (IQR, 1.00–8.50) [L0] to 4.5 (IQR, 0.75–9.00; p>0.01) [L1] and by 2 points to 2.00 (IQR, 1.00–7.00; p=0.012) [L2].

A response was considered to be positive when the score on the hyperactivity/irritability subscale improved by ≥25%. A significant improvement was observed for hyperactivity (51.7%), irritability (35.5%), and logorrhea (50%), with no sedative effect (lethargy subscale) (Table 3). The CGI-S score was much improved or very much improved in 73% of cases at the end of the study period.

An overall improvement in the global index of adaptive behavior (ABAS II) was observed, at the final period of treatment, especially in self-care, increasing by 2 points from 3.00 (IQR, 2.75–4.00) [L0] to 4.00 (IQR, 3.00–5.00; p=0.012) [L1] during the first month of treatment and to 4.50 (IQR, 3.75–5.25; p<0.01) [L2]. Self-direction improved by 4 points from 71.00 (IQR, 55.50–78.50) [L0] to 75.00 (IQR, 55.50–81.50) [L0] to 74.00 (IQR, 62.50–85.50; p=0.064) [L2] (Table 4).

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**Table 3. Behavioral changes.**

| Test scores       | L0            | IQR    | L1            | IQR    | L2            | IQR    | p  | Δ   | P  | Δ   |
|-------------------|---------------|--------|---------------|--------|---------------|--------|----|-----|----|-----|
| Aberrant Behavior Checklist (ABC) |               |        |               |        |               |        |    |     |    |     |
| Hyperactivity     | 14.50         | 3.50–25.50 | 12.50         | 4.75–23.50 | 7.00          | 3.00–16.50 | >0.1 | =   | 0.063 | ↓   |
| Lethargy          | 9.50          | 4.50–19.00 | 11.50         | 3.00–15.75 | 10.00         | 1.50–16.75 | >0.1 | =   | >0.1  | =   |
| Stereotypy        | 4.50          | 1.50–7.75  | 2.50          | 2.00–9.25  | 2.50          | 0.75–6.25  | <0.025 | ↓   | >0.1  | =   |
| Irritability      | 15.50         | 4.00–25.25 | 13.50         | 7.00–27.50 | 10.00         | 4.50–26.50 | >0.1 | =   | 0.049 | ↓   |
| Logorrhea         | 4.00          | 1.00–8.50  | 4.50          | 0.75–9.00  | 2.00          | 1.00–7.00  | >0.1 | =   | 0.012 | ↓   |

L0: Baseline evaluation, L1: Second evaluation (4 weeks), L2: Final evaluation (12 weeks).

Wilcoxon signed-rank test. Significance was set at p=0.10. IQR, interquartile range; Δ, change.

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**Table 4. Adaptive behavior changes.**

| Test scores       | L0            | IQR    | L1            | IQR    | L2            | IQR    | p  | Δ   | P  | Δ   |
|-------------------|---------------|--------|---------------|--------|---------------|--------|----|-----|----|-----|
| Adaptive Behavior Assessment System (ABAS-II) |               |        |               |        |               |        |    |     |    |     |
| Self-care         | 89.00         | 83.75–93.25 | 88.00         | 81.00–94.50 | 91.00         | 81.50–96.25 | >0.1 | =   | 0.076 | ↑   |
| Self-direction    | 71.00         | 55.50–78.50 | 72.00         | 51.00–79.50 | 75.00         | 55.50–84.50 | >0.1 | =   | 0.033 | ↑   |
| Social            | 71.00         | 65.50–81.50 | 72.00         | 59.00–78.50 | 74.00         | 62.50–85.50 | >0.1 | =   | 0.064 | ↑   |

Wilcoxon signed-rank test. Significance was set at p=0.10. IQR, interquartile range; Δ, change.
Psychomotor coordination

The results showed an improvement in psychomotor speed and eye-hand coordination for the nondominant hand between L0 and L1 (p<0.023) (Table 7), but not for the rest.

Executive function

A statistically significant difference was observed for the number of movements used to solve the problem and for the total number of correctly solved problems (TOL-DX), especially during the first month of treatment. This tended to remain unchanged (from 6.00 [L0] to 7.00 [L1] [p=0.072] and from 7.00 to 7.00 [L2] [p=0.043]). The most relevant aspects from a neuropsychological point of view would be the improvement associated with the reaction time processes, with a faster execution speed (Table 8). According to the parents’ opinion (BRIEF-P), treatment did not lead to an improvement in the regulation of behavior.

Table 5. Changes in attention, impulsivity, and alertness.

| Test scores | L0 Median | L1 Median | L2 Median | L0 versus L1 p | L1 versus L2 p |
|-------------|-----------|-----------|-----------|----------------|----------------|
| Conners Kiddie Continuous Performance Test, Second Edition (K-CPT 2) | | | | | |
| Detectability | 64.00 | 51.00 | 53.00 | 0.014 | >0.1 |
| Commission errors | 52.00 | 41.00 | 43.00 | 0.021 | >0.1 |
| Perseverations | 50.00 | 48.00 | 49.00 | 0.019 | >0.1 |
| HRT SD | 63.00 | 50.00 | 51.00 | 0.036 | >0.1 |
| WAIS III (Direct Digits) | | | | | |
| Span | 3.00 | 4.50 | 5.25 | 0.012 | <0.035 |
| Effectiveness | 4.00 | 5.25 | 5.25 | 0.008 | <0.076 |
| Color Trail Test, CTT | | | | | |
| CTT1 Time | 60.00 | 49.50 | 48.00 | 0.020 | >0.1 |
| CTT2 Time | 130.00 | 112.50 | 101.50 | 0.026 | >0.1 |
| Interf Index | 1.10 | 1.69 | 0.66 | >0.1 | <0.01 |

Wilcoxon signed-rank test. Significance was set at p=0.10. IQR, interquartile range; ∆, change.

Table 6. Changes in memory ability.

| Test scores | L0 Median | L1 Median | L2 Median | L0 versus L1 p | L1 versus L2 p |
|-------------|-----------|-----------|-----------|----------------|----------------|
| Repeatable Battery for the Assessment of Neuropsychological Status (R-BANS) | | | | | |
| Total A1-A4 | 20.00 | 25.00 | 24.00 | 0.008 | = |
| Rec demo | 4.00 | 5.00 | 5.00 | 0.044 | = |
| Recon | 20.00 | 19.00 | 18.00 | = | 0.063 |
| F Recon | 0.00 | 2.00 | 2.00 | = | 0.063 |

Wilcoxon signed-rank test. Significance was set at p=0.10. IQR, interquartile range; ∆, change.
Table 7. Psychomotor speed and manual dexterity.

| Test scores          | L0       | IQR     | L1       | IQR     | L2       | IQR     | p   | Δ    | p   | Δ    |
|----------------------|----------|---------|----------|---------|----------|---------|-----|------|-----|------|
| **Purdue Pegboard Test** |          |         |          |         |          |         |     |      |     |      |
| Right hand           | 9.00     | 7.00–13.00 | 10.00   | 6.00–13.00 | 9.00   | 6.00–12.00 | >0.1 | = | >0.1 | =
| Left hand            | 8.00     | 7.00–11.00 | 10.00   | 7.00–12.00 | 10.00  | 6.00–13.00 | 0.023 | ↑ | >0.1 | =

Wilcoxon signed-rank test. Significance was set at \( p=0.10 \).

IQR, interquartile range; \( \Delta \), change.

Table 8. Executive function changes.

| Test scores          | L0       | IQR     | L1       | IQR     | L2       | IQR     | p   | Δ    | p   | Δ    |
|----------------------|----------|---------|----------|---------|----------|---------|-----|------|-----|------|
| **Tower of London DX (TOL-DX)** |          |         |          |         |          |         |     |      |     |      |
| Correct              | 6.00     | 4.50–7.00 | 7.00     | 6.00–8.00 | 7.00    | 5.00–8.50 | 0.072 | ↑ | 0.043 | ↑
| Movements            | 24.00    | 12.00–38.00 | 14.00   | 6.50–20.50 | 18.00  | 3.00–26.00 | 0.042 | ↓ | 0.044 | ↓
| Start time           | 27.00    | 18.50–42.00 | 24.00   | 16.00–38.00 | 21.00  | 14.50–27.50 | >0.1 | = | 0.092 | ↓
| Execution time       | 110.00   | 83.00–326.00 | 100.00  | 75.50–155.50 | 87.00  | 59.00–223.50 | >0.1 | = | 0.039 | ↓
| Total time           | 132.00   | 94.00–372.00 | 126.00  | 93.00–189.00 | 110.00 | 73.50–275.50 | >0.1 | = | 0.039 | ↓
| **Behavior Rating Inventory of Executive Function (BRIEF)** |          |         |          |         |          |         |     |      |     |      |
| Inhibit              | 21.00    | 14.00–25.00 | 18.00   | 12.00–26.50 | 17.00  | 13.50–25.50 | >0.1 | = | 0.019 | ↓
| Shift                | 17.00    | 13.50–20.50 | 18.00   | 14.00–19.50 | 17.00  | 12.00–20.00 | >0.1 | = | >0.1 | =
| Emotion              | 20.00    | 14.50–27.00 | 20.00   | 16.00–23.00 | 18.00  | 14.00–24.00 | >0.1 | = | 0.024 | ↓
| Behavior Regulation Index | 59.00 | 41.00–70.50 | 57.50   | 46.00–67.50 | 55.00  | 44.50–71.00 | >0.1 | = | 0.017 | ↓

Wilcoxon signed-rank test. Significance was set at \( p=0.10 \).

IQR, interquartile range; \( \Delta \), change.

Tolerability and safety

The tolerability to treatment was excellent in 28 patients (90%) who reported no relevant adverse effects. Two patients (6.6%) reported mild gastrointestinal complaints (nausea and diarrhea). Five patients reported sedation, which presented as ‘calmness’, with no tiredness, heaviness, or alteration in reflexes, and this was considered positively by those affected. It was not necessary to stop treatment in any case.

Discussion

Social integration of people with disabilities is increasingly facilitated by programs and initiatives that reduce dependency and improve well-being. However, cognitive impairment and challenging behavior reduce the quality of life of patients and their caregivers. These conditions are shared by various neurodevelopmental disorders, such as ADHD, ASD, and BIF/IDD. Despite the availability of pharmacological strategies (antipsychotic, anxiolytics, and psychostimulants), cognitive, behavioral, and metabolic adverse effects are a major limitation to prescription and alternative approaches have been sought, including behavioral therapy and drugs acting on the GABA system in the brain. GABAergic mechanisms are involved in specific behavior patterns, physiological functions, and, possibly, the origin of some mental disorders. Cortical GABA regulates a number of cognitive functions, including attention and executive function, and is dysregulated in persons with a clinical diagnosis of ADHD, ASD, and BIF/IDD.

The primary function of GABA as the brain’s major inhibitory neurotransmitter is to prevent overstimulation and, consequently, to improve attentional processes. This complex phenomenon implies not only impaired attention but also...
persistent damage to impulse control and increased locomotor activity in patients with IDD. One of the objectives of this study was to evaluate the effectiveness of GB6 on behavior and cognitive performance.

Our findings provide evidence for an improvement in challenging behaviors, especially those related to hyperactivity. Given that hyperactivity decreased (51.7%), as did logorrhea (50%) and irritability (35.5%), we can state that, from a behavioral point of view, there is a general ‘inhibition’ of behavior. Such a ‘calmed state’ has no sedative effect, as shown by the results in the lethargy subscale.

As for cognition, we obtained better results on processing speed in the form of a cognitive profile characterized by better reaction time with fewer errors. This fact is closely associated with the gain in attentional skills. Inconsistent response speed is sometimes indicative of inattentiveness, and our results suggest that the patients were engaged and processed stimuli more efficiently. This improvement in the consistency of speed across various test evaluations (sustained and shared attention) indicates less interference in the performance of tasks and fewer errors in the task. Therefore, inhibitory control is improved. This performance is maintained over several evaluations.

The ability to focus on the task at hand while ignoring distractions is crucial for adaptive behavior and other domains in skilled performance and is potentially one of the reasons for the improvement reported by parents in self-care, self-direction, and social skills.

Executive function has been defined as ‘neurocognitive processes that maintain an appropriate problem-solving set to attain a future goal’. Different neuropsychological theories have suggested deficient executive function as one of the main characteristics of ADHD in people who do not have IDD. It is well known that a number of theories explain ASD as a dysexecutive disorder. Additionally, in patients with BIF and mild IDD, the executive function has been shown to be the most impaired area regardless of the other two diagnoses. Therefore, the population of this study experienced, a priori, major dysexecutive syndrome because they all had a combination comprising ASD, ADHD, and/or BIF/IDD, all of which are neurodevelopmental disorders associated with dysfunction of the frontostriatal system. The TOL\textsuperscript{DXtm} evaluates difficulties with planning and nonverbal problem-solving, which are associated with frontal lobe dysfunction, especially in the right dorsolateral prefrontal cortex, cingulate cortex, and frontostriatal system. According to our executive TOL\textsuperscript{DXtm} results, statistically significant findings were obtained for the number of movements used to solve the problem and for the total number of correctly solved problems, especially during the first month of treatment. From a neuropsychological point of view, we emphasize not only the improvement in this variable but also the faster reaction times recorded. The authors speculated that this might be the result of an increase in processing speed but not of psychomotor development (the Purdue test showed an improvement in the nondominant hand).

There were no significant relationships between parents’ ratings of the executive syndrome (BRIEF-P) and executive improvement in the evaluations. Interestingly, according to the parents’ point of view, no association was observed between performance in executive measures, although better self-regulation in behavior was reported.

The association between attention and memory is well documented. This investigation revealed that the mean values of learning total and delayed recall of words increase after treatment.

Taken together, our findings suggest that findings for both executive functioning (TOL\textsuperscript{DXtm} and amnestic processes (RBANS) improved owing to their association with attentional processes.

This pilot study has a number of limitations that need to be considered. Firstly, the small number of patients included in the study limits the strength of the statistical analyses, making it more difficult to identify statistically significant changes. It also precludes subgroup comparisons because the small numbers increase the likelihood of finding false-positive results (i.e. due to chance). In additional, the small number of patients makes it difficult to investigate tolerability and safety, especially for less common or rare adverse events. The duration of the study was also too short to assess long-term efficacy and safety. Finally, the uncontrolled nature of the clinical study increases the risk that the results might be influenced by bias. Despite these limitations, the majority of patients were classified as having a positive response and requested continuation of treatment at study end and show continued benefit at 6 and 12 months (data not shown).

Prospective research on developmental differences in GB6 responses, examination of differences in GABA metabolism in adults, comparison of different GABA agents, and different trial designs are all needed to better understand contrasting results in the behavior disorders treatment literature. This should help us further elucidate agent-specific effects in different types of behavior disorders. For future investigation, we highlight the need for long-term efficacy and safety data in large study groups. It would also be interesting to have results from research on combined therapies, such as combined treatment with GB6 as an augmentative or preparatory lead-in to cognitive-behavior therapy. Finally, additional work examining developmental differences in GB6 treatment response in people with intellectual disabilities is needed.

**Conclusion**

In this pilot study, GB6 was effective and well tolerated in cases of ADHD and challenging behavior in young adults with borderline-to-mild BIF/IDD. Given the small number of patients involved, and the short duration and uncontrolled nature of the study, these results should be viewed cautiously, but they do merit further investigation in a larger well-controlled long-term clinical trial.
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