DRUGS IN CONTEXT
RIGOROUS • RAPID • RESPONSIVE

A continuous publication, open access, peer-reviewed journal

ACCESS ONLINE

ORIGINAL RESEARCH

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

Ramón Novell MD, Susanna Esteba-Castillo PhD, Emili Rodriguez PhD

Specialized Service in Mental Health and Intellectual Disability (SEMSDI), Parc Hospitalàri Martí i Julià, Instituto de Asistencia Sanitaria, Girona, Spain

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

Novell R, Esteba-Castillo S, Rodriguez E. 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. Drugs in Context 2020; 9: 212601. DOI: 10.7573/dic.212601

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]; the short- and long-term effectiveness of antipsychotics for challenging behavior remains a topic of discussion.[7–10] Moreover, many antipsychotics have short- and long-term adverse effects[8–16] 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.[19] 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.[20,21] In addition, the consumption of anxiolytics and hypnotics in Europe is increasing,[22,23] and approximately 13% of patients with intellectual disability experience the behavioral adverse effects of benzodiazepine. The four most frequently reported behavioral side effects are aggression, irritability, hyperactivity, and agitation.[24]

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,[25–28] stress,[29,30] post-traumatic stress disorder,[31,32] depression,[33,34] ADHD,[35] autism,[36–40] epilepsy,[41] insomnia,[42,43] and movement disorders such as Tourette's syndrome,[44] Parkinson's disease,[45] and tardive dyskinesia.[46] 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.[47]

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.[48] 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.[49]

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.[50]

An effective intervention for many hyperactive children, besides methylphenidate and other psychostimulants, is the use of vitamin B6 (pyridoxine) and magnesium (Mg^{2+}).[51]

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.[52] Therefore, while Mg^{2+} has been shown to be a nonspecific calcium channel inhibitor, it could act as an *N*-methyl-D-aspartate channel inhibitor.[53] Similarly, Mg^{2+} could influence catecholamine signaling in the brain.[54] Intraerythrocytic Mg^{2+} depletion has been observed in ADHD patients, and increased hyperactivity and decreased attention at school were associated with decreases in Erc-Mg^{2+} 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.[55]

Gamalate® B6 (GB6) is formulated as a coated tablet containing: magnesium glutamate hydrobromide (MGHB) 75 mg, GABA 75 mg, γ-amino-β-hydroxybutyric 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.[56]

Treatment with GB6 has proven effective in fibromyalgia by reducing pain and fatigue.[57] It also improves symptoms of anxiety[58,59] and tension headache accompanied by anxiety or depression by inducing a euthymic effect.[60] Numerous studies have demonstrated the efficacy of GB6 on the intellectual performance of children with and without intellectual disabilities.[61–67] 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).[68]

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.[69] 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),[70] the Declaration of Helsinki (AMM, Seoul, October 2008),[71] and Law 14/2007 on Biomedical Research published in the Spanish Official Gazette.[72] 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,[73] 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[74] 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),[75] 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.

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)

Specific neuropsychological testing

Intellectual quotient

We applied the Kaufman Brief Intelligence Test, Second Edition (KBIT-2),[76] 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)[77] 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)[78] was used to evaluate sustained attention as well as processing speed, shared attention, and mental flexibility.

We also applied the Memory for Digit Span assessment (Digits Forward), a component of the Wechsler Intelligence for Adults (WAIS IV),[79] 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)[80] 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,[81] 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 (TOL^{DXtm}) for persons with IDD was used.[82,83] The planning sequence begins with an objective, mentally rehearsing, applying one's chosen strategy, and finally appraising whether or not the objective is achieved.[84] The Behavior Rating Inventory of Executive Function (BRIEF)[85] 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.

Table 2. Demographic characteristics of adults with IDD and attention-deficit hyperactivity disorder.

	n	Median	IQR
Age (years)	30	20.25	16.00–24.50
Men	20	66.6%	
Women	10	33.4%	
KBIT-2 Intelligence Quotient	30	77.50	67.00–88.00
Autism diagnosis	12	40%	

IQR, Interquartile range.

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

(IQR, 3.50–25.50) [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 89.00 (IQR, 83.75–93.2) [L0] to 91.00 (IQR, 81.50–96.25; $p=0.076$) [L2]. Self-direction improved by 4 points from 71.00 (IQR, 55.50–78.50) [L0] to 75.00 (IQR, 55.50–78.50; $p=0.033$) [L2], and social skills increased 3 points from 71.00 (IQR, 65.50–81.50) [L0] to 74.00 (IQR, 62.50–85.50; $p=0.064$) [L2] (Table 4).

Secondary outcome

Attention, impulsivity, and alertness

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;

Table 3. Behavioral changes.

Test scores	L0		L1		L2		L0 *versus* L1		L1 *versus* L2	
	Median	IQR	Median	IQR	Median	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.

Table 4. Adaptive behavior changes.

Test scores	L0		L1		L2		L0 *versus* L1		L1 *versus* L2	
	Median	IQR	Median	IQR	Median	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.

p=0.035) [L2] at the end of the treatment. Consequently, effectiveness also improved from 4.00 (IQR, 2.75–5.25) [L0] to 5.00 (IQR, 3.00–7.00; p<0.008) [L1] during the first month and to 5.25 (IQR, 3.25–7.25; p=0.076) [L2] at the end of the treatment (Table 5). The results for the Color Trail Test revealed a decrease in the execution time of CTT1 (measure of sustained attention) from 60.00 (IQR, 35.25–86.75) [L0] to 48.00 (IQR, 37.75–95.25; p=0.020) [L2] and in CTT2 (measure of shared attention) from 130.00 (IQR, 80.50–150.00) [L0] to 101.50 (IQR, 66.25–168.50; p=0.026) [L2] after 2 months of treatment (Table 5).

Memory

In the first month, the treatment led to an improvement in the total items of the verbal learning list from RBANS (improving from 20 words to 25) (p<0.008), as well as in free delayed (p=0.044). It is important to point out that we applied different versions of RBANS in each evaluation (Table 6).

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		L1		L2		L0 *versus* L1		L1 *versus* L2	
	Median	IQR	Median	IQR	Median	IQR	*p*	Δ	*p*	Δ
Conners Kiddie Continuous Performance Test, Second Edition (K-CPT 2)										
Detectability	64.00	46.00–76.00	51.00	45.00–65.00	53.00	45.00–63.00	0.014	↓	>0.1	=
Commission errors	52.00	41.00–72.00	41.00	38.00–57.00	43.00	37.00–52.00	0.021	↓	>0.1	=
Perseverations	50.00	48.00–78.00	48.00	46.00–60.00	49.00	46.00–55.00	0.019	↓	>0.1	=
HRT SD	63.00	47.00–77.00	50.00	43.00–65.00	51.00	46.00–63.00	0.036	↓	>0.1	=
WAIS III (Direct Digits)										
Span	3.00	2.75–4.00	4.00	3.00–5.00	4.50	3.75–5.25	0.012	↑	<0.035	↑
Effectiveness	4.00	2.75–5.25	5.00	3.00–7.00	5.25	3.25–7.25	0.008	↑	<0.076	↑
Color Trail Test, CTT										
CTT1 Time	60.00	35.25–86.75	49.50	28.50–64.75	48.00	37.75–95.25	0.020	↓	>0.1	=
CTT2 Time	130.00	80.50–150.00	112.50	71.00–156.75	101.50	66.25–168.50	0.026	↓	>0.1	=
Interf Index	1.10	0.59–1.72	1.69	0.49–1.12	0.66	0.40–1.12	>0.1	=	<0.01	↓

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

Table 6. Changes in memory ability.

Test scores	L0		L1		L2		L0 *versus* L1		L1 *versus* L2	
	Median	IQR	Median	IQR	Median	IQR	*p*	Δ	*p*	Δ
Repeatable Battery for the Assessment of Neuropsychological Status (R-BANS)										
Total A1-A4	20.00	16.00–26.50	25.00	18.50–31.50	24.00	17.00–25.00	0.008	↑		=
Rec demo	4.00	3.00–5.50	5.00	4.00–7.50	5.00	3.50–7.00	0.044	↑		=
Recon	20.00	17.50–20.00	19.00	17.00–20.00	18.00	16.00–19.50		=	0.063	↓
F Recon	0.00	0.00–2.50	1.00	0.00–3.00	2.00	0.50–4.00		=	0.063	↓

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

Table 7. Psychomotor speed and manual dexterity.

Test scores	L0		L1		L2		L0 *versus* L1		L1 *versus* L2	
	Median	IQR	Median	IQR	Median	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; Δ, change.

Table 8. Executive function changes.

Test scores	L0		L1		L2		L0 *versus* L1		L1 *versus* L2	
	Median	IQR	Median	IQR	Median	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; Δ, 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[86] 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'.[87] Different neuropsychological theories have suggested deficient executive function as one of the main characteristics of ADHD in people who do not have IDD.[88] 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^{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^{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^{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 addition, 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.

Contributions: All authors contributed extensively to the work presented in this paper. All authors have contributed significantly to the conception, design, data collection, and execution of the study. All authors participated in drafting and/or reviewing the manuscript and have approved its submission. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: The authors declare that they have no conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at https://www.drugsincontext.com/wp-content/uploads/2019/12/dic.212601-COI.pdf

Acknowledgments: Writing and editorial assistance was provided by Content Ed Net (Madrid, Spain).

Funding declaration: Funding for editorial assistance was provided by Ferrer Internacional SA (Barcelona, Spain). No external funding was received for the research work.

Article URL: https://www.drugsincontext.com/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/

Correspondence: Ramon Novell, Specialized Service in Mental Health and Intellectual Disability (SEMSDI), Parc Hospitalàri Martí i Julià, Instituto de Asistencia Sanitaria, Girona, Spain. ramon.novell@ias.cat

Provenance: invited; externally peer reviewed.

Submitted: 1 June 2019; **Peer review comments to author:** 18 July 2019; **Revised manuscript received:** 12 December 2019; **Accepted:** 12 December 2019; **Publication date:** 23 January 2020.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

For all manuscript and submissions enquiries, contact the Editor-in-Chief gordon.mallarkey@bioexcelpublishing.com

For all permissions, rights, and reprints, contact David Hughes david.hughes@bioexcelpublishing.com

References

1. Novell R, Rueda P, Salvador S. Mental Health and behavior disorders in people with intellectual disabilities. 2003. Colección FEAPS. http://www.plenainclusion.org/sites/default/files/libro_saludmental.pdf. Accessed December 12, 2019.
2. Novell R, Nadal M, Smilges A, Pascual L, Pujol J. Aging and intellectual disability in Catalonia. SENECA Report 2005–2008. Barcelona: Federación APPS; 2008.
3. Cooper SA, Smiley E, Morrison J, Williamson A, Allan L. Mental ill-health in adults with intellectual disabilities: prevalence and associated factors. *Br J Psychiatry.* 2007;190:27–35. https://doi.org/10.1192/bjp.bp.106.022483
4. Emerson E, Moss S, Ciernan C. The relationship between challenging behaviour and psychiatric disorders in people with severe intellectual disability. In: Bouras N, ed. Psychiatric and behavioural disorders in developmental disabilities and mental retardation. Cambridge: Cambridge University Press, 38–48; 1999.
5. McDougle CJ, Scahill L, Aman MG, et al. Risperidone for the core sympton domains of autism: results from the study by the autism network of the research units on pedriatic psychopharmacology. *Am J Psychiatry.* 2005;162(6):1142–1148. https://doi.org/10.1176/appi.ajp.162.6.1142
6. Ichikawa H, Mikami K, Okada T, et al. Aripiprazole in the treatment of irritability in children and adolescents with autism spectrum disorder: a randomized, double-blind, placebo-controlled study. *Child Psychiatry Hum Dev.* 2017;48(5):796–806. https://doi.org/10.1007/s10578-016-0704-x
7. Tyrer P, Oliver-Africano PC, Ahmed Z, et al. Risperidone, haloperidol, and placebo in the treatment of aggressive challenging behaviour in patients with intellectual disability: a randomised controlled trial. *Lancet*. 2008;371(9606):57–63. https://doi.org/10.1016/S0140-6736(08)60072-0
8. de Kuijper G, Evenhuis H, Minderaa RB, Hoekstra PJ. Effects of controlled discontinuation of long-term used antipsychotics for behavioural symptoms in individuals with intellectual disability. *J Intellect Disabil Res*. 2014;58(1):71–83. https://doi.org/10.1111/j.1365-2788.2012.01631.x
9. de Kuijper GM, Hoekstra PJ. An Open-Label Discontinuation trial of long-term, off-label antipsychotic medication in people with intellectual disability: determinants of success and failure. *J Clin Pharmacol*. 2018;58(11):1418–1426. https://doi.org/10.1002/jcph.1271

10. Ramerman L, de Kuijper G, Scheers T, Vink M, Vrijmoeth P, Hoekstra PJ. Is risperidone effective in reducing challenging behaviours in individuals with intellectual disabilities after 1 year or longer use? A placebo-controlled, randomised, double-blind discontinuation study. *J Intellect Disabil Res*. 2019;63(5):418–428. https://doi.org/10.1111/jir.12584
11. Frighi V, Stephenson MT, Morovat A, et al. Safety of antipsychotics in people with intellectual disability. *Br J Psychiatry*. 2011;199(4):289–295. https://doi.org/10.1192/bjp.bp.110.085670
12. Campbell M, Armenteros JL, Malone RP, Adams PB, Eisenberg ZW, Overall JE. Neuroleptic-related dyskinesias in autistic children: a prospective, longitudinal study. *J Am Acad Child Adolesc Psychiatry*. 1997;36(6):835–843. https://doi.org/10.1097/00004583-199706000-00022
13. Room B. Timmermans O, Roodbol P. The prevalence and risk factors of the metabolic syndrome in inpatients with intellectual disability. *J Intellect Disabil Res*. 2016;60(6):594–605. https://doi.org/10.1111/jir.12282
14. Winter CF, Magilsen KW, van Alfen JC, Willemsen SP, Evenhuis HM. Metabolic syndrome in 25% of older people with intellectual disability. *Fam Pract*. 2011;28(2):141–144. https://doi.org/10.1093/fampra/cmq079
15. Azimi K, Raina P, Lunski Y. Occurrence of metabolic syndrome in inpatients with intellectual disability treated with atypical antipsychotics. *J Dev Disabil* 2011;17(2):48–50.
16. Azumi K, Ischizuka S, Fujii M, Sasaki H. Antipsychotics and cognitive function. *Psychogeriatrics*. 2011;11(2):79–82. https://doi.org/10.1111/j.1479-8301.2011.00372.x
17. Sayal K, Prasad V, Dalay D, Ford T, Coghill D. ADHD in children and young people: prevalence, care pathways, and service provision. *Lancet Psychiatry*. 2018;5(2):175–186. https://doi.org/10.1016/S2215-0366(17)30167-0
18. NICE Guide Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults. 2008. Clinical Guideline 72. National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/ng87. Accessed December 12, 2019.
19. Bukstein O. Attention deficit hyperactivity disorder in adults: Epidemiology, pathogenesis, clinical features, course, assessment, and diagnosis. UpToDate, 8 February 2018. Web. 9 February 2018. https://www.uptodate.com/contents/attention-deficit-hyperactivity-disorder-in-adults-epidemiology-pathogenesis-clinical-features-course-assessment-and-diagnosis. Accessed December 12, 2019.
20. Rey JM, Sawyer MG. Are psychostimulant drugs being used appropriately to treat child and adolescent disorders? *Br J Psychiatry*. 2003;182:284–286. https://doi.org/10.1192/bjp.182.4.284
21. Wei Y, Zhu Y, Liu W, Bussing R, Winterstein AG. Prevalence of and factors associated with long-term concurrent use of stimulants and opioids among adults with attention-deficit/hyperactivity disorder. *JAMA Network Open*. 2018;1(4):e181152. https://doi.org/10.1001/jamanetworkopen.2018.1152
22. Axmon A, Kristensson J, Ahlström G, Midlöv P. Use of antipsychotics, benzodiazepine derivatives, and dementia medication among older people with intellectual disability and/or autism spectrum disorder and dementia. *Res Dev Disabil*. 2017;62:50–57. https://doi.org/10.1016/j.ridd.2017.01.001
23. Encuesta Nacional de Salud 2011-2012. Ministerio de Consumo y Bienstar Social, Gobierno de España. https://www.mscbs.gob.es/estadEstudios/estadisticas/encuestaNacional/encuesta2011.htm. Accessed December 12, 2019.
24. Kalachnick JE, Hanzel TE, Sevenich R, Harder SR. Benzodiazepine behavioral side effects: review and implications for individuals with mental retardation. *Am J Men Retard*. 2002;107(5):376–410. https://doi.org/10.1352/0895-8017(2002)107%3C0376:BBSERA%3E2.0.CO;2
25. Gilpin NW. Corticotropin-releasing factor (CRF) and neuropeptide Y (NPY): effects on inhibitory transmission in central amygdala, and anxiety- & alcohol-related behaviors. *Alcohol*. 2012;46(4):329–337. https://doi.org/10.1016/j.alcohol.2011.11.009
26. Zhang Z, Fan Q, Bai Y, Wang Z, Zhang H, Xiao Z. Brain Gamma-Aminobutyric Acid (GABA) concentration of the prefrontal lobe in unmedicated patients with obsessive-compulsive disorder: a research of magnetic resonance spectroscopy. *Shanghai Arch Psychiatry*. 2016;28(5):263–270. https://doi.org/10.11919/j.issn.1002-0829.216043
27. Levar N, van Leeuwen JMC, Puts NAJ, Denys D, van Wingen GA. GABA concentrations in the anterior cingulate cortex are associated with fear network function and fear recovery in humans. *Front Hum Neurosci*. 2017;11:202. https://doi.org/10.3389/fnhum.2017.00202
28. Skorzewska A, Wislowska-Stanek A, Lehner M, et al. Corticotropin releasing factor receptor 1 antagonist differentially inhibits freezing behavior and changes gamma-aminobutyric acidergic activity in the amygdala in low- and high-anxiety rats. *J Physiol Pharmacol*. 2017;68(1):35–46. https://www.ncbi.nlm.nih.gov/pubmed/28456768
29. Szczepanska-Sadowska E, Cudnoch-Jedrzejewska A, Ufnal M, Zera T. Brain and cardiovascular diseases: common neurogenic background of cardiovascular, metabolic and inflammatory diseases. *J Physiol Pharmacol*. 2010;61(5):509–521. https://www.ncbi.nlm.nih.gov/pubmed/21081794
30. Campos AC, Fogaça MV, Scarante FF, et al. Plastic and neuroprotective mechanisms involved in the therapeutic effects of cannabidiol in psychiatric disorders. *Front Pharmacol*. 2017;8:269. https://doi.org/10.3389/fphar.2017.00269

31. Vaiva G, Thomas P, Ducrocq F, et al. Low posttrauma GABA plasma levels as a predictive factor in the development of acute posttraumatic stress disorder. *Biol Psychiatry.* 2004;55(3):250–254. https://doi.org/10.1016/j.biopsych.2003.08.009
32. Vaiva G, Boss V, Ducrocq F, et al. Relationship between posttrauma GABA plasma levels and PTSD at 1-year follow-up. *Am J Psychiatr.* 2006;163(8):1446–1448. https://doi.org/10.1176/ajp.2006.163.8.1446
33. Zhu Z, Wang G, Ma K, Cui S, Wang JH. GABAergic neurons in nucleus accumbens are correlated to resilience and vulnerability to chronic stress for major depression. *Oncotarget.* 2017;8(22):35933–35945. https://doi.org/10.18632/oncotarget.16411
34. Romeo B, Choucha W, Fossati P, Rotge JY. Meta-analysis of central and peripheral γ-aminobutyric acid levels in patients with unipolar and bipolar depression. *J Psychiatry Neurosci.* 2018;43(1):58–66. https://doi.org/10.1503%2Fjpn.160228
35. Edden RAE, Crocetti D, Zhu H, Gilbert DL, Mostofsky SH. Reduced GABA concentration in attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry.* 2012;69(7):750–753. https://doi.org/10.1001/archgenpsychiatry.2011.2280
36. Coghlan S, Horder J, Inkster B, Mendez MA, Murphy DG, Nutt DG. GABA system dysfunction in autism and related disorders: from synapse to symptoms. *Neurosci Biobehav Rev.* 2012;36(9):2044–2055. https://doi.org/10.1016/j.neubiorev.2012.07.005
37. Fatemi SH, Reutiman TJ, Folsom TD, Rustan OG, Rooney RJ, Thuras PD. Downregulation of GABAA receptor protein subunits in superior frontal cortex of subjects with autism. *J Autism Dev Disord.* 2014;44(8):1833–1845. https://doi.org/10.1007/s10803-014-2078-x
38. Puts NAJ, Wodka EL, Harris AD, et al. Reduced GABA and altered somatosensory function in children with autism spectrum disorder. *Autism Res.* 2017;10(4):608–619. https://doi.org/10.1002/aur.1691
39. Pizzarelli R, Cherubini E. Alterations of GABAergic signaling in autism spectrum disorders. *Neural Plat.* 2011;2011:297153. https://doi.org/10.1155/2011/297153
40. Ajram LA, Horder J, Mendez MA, et al. Shifting brain inhibitory balance and connectivity of the prefrontal cortex of adults with autism spectrum disorders. *Trans Psychiatry.* 2017;7(5):e1137. https://doi.org/10.1038/tp.2017.104
41. Czuczwar SJ, Patsalos PN. The new generation of GABA enhancers. Potential in the treatment of epilepsy. *CNS Drugs.* 2001;15(5):339–350. https://doi.org/10.2165/00023210-200115050-00001
42. Walsh JK. Understanding GABA and its relation to insomnia and therapeutics. *J Clin Sleep Med.* 2006;2(2):S5–S6. https://www.ncbi.nlm.nih.gov/pubmed/17557500
43. Plante DT, Jensen JE, Winkelman JW. The role of GABA in primary insomnia. *Sleep.* 2012;35(6):741–742. https://doi.org/10.5665/sl 2001;31(2):247–248. https://www.ncbi.nlm.nih.gov/pubmed/11450824
44. Lerner A, Bagic A, Simmons JM, et al. Widespread abnormality of the γ-aminobutyric acid-ergic system in Tourette syndrome. *Brain.* 2012;135(Pt 6):1926–1936. https://doi.org/10.1093/brain/aws104
45. Schapira AHV, Bezard E, Brotchie J, et al. Novel pharmacological targets for the treatment of Parkinson's disease. *Nat Rev Drug Discov.* 2006;5(10):845–854. https://doi.org/10.1038/nrd2087
46. Casey DE, Gerlach J, Magelund G, Christensen TR. gamma-Acetylenic GABA in tardive dyskinesia. *Arch Gen Psychiatry.* 1980;37(12):1376–1379. https://doi.org/10.1001/archpsyc.1980.01780250062007
47. Gatto CL, Broadie K. Genetic controls balancing excitatory and inhibitory synaptogenesis in neurodevelopmental disorder model. *Front. Synaptic Neurosci.* 2010;2:4. https://dx.doi.org/10.3389%2Ffnsyn.2010.00004
48. Hussman JP. Suppressed GABAergic inhibition as a common factor in suspected etiologies of autism. *J Autism Dev Disord.* 2001;31(2):247–248. https://doi.org/10.1023/a:1010715619091
49. Robertson CE, Ratai EM, Kanwisher N. Reduced GABAergic action in the autistic brain. *Curr Biol.* 2016;26(1):80–85. https://doi.org/10.1016/j.cub.2015.11.019
50. Lee JS, Lee JD, Park HJ, et al. Is the GABA system related to the socil competence improvement effect of aripiprazole? An (18) F-fluoroflumazenil PET study. *Psychiatry Investig.* 2013;10(1):75–80. https://doi.org/10.4306/pi.2013.10.1.75
51. Murza KA, Pavelko SL, Malani MD, Nye C. Vitamin B6-magnesium treatment for autism: the current status of the research. *Magnes Res.* 2010;23(2):115–117. https://doi.org/10.1684/mrh.2010.0209
52. Feillet-Coudray C, Coudray C, Wolf FI, Henrotte JG, Rayssigier Y, Mazur A. Magnesium metabolism in mice selected for high and low erythrocyte magnesium levels. *Metabolism.* 2004;53(5):660–665. https://doi.org/10.1016/j.metabol.2003.12.014
53. Vink R. Magnesium in traumatic brain injury: past findings and futures directions. In Rayssiguier Y, Mazur A, Durlach J, eds. *Advances in Magnesium Research: Nutrition and Health*. London: John Libbey Company, 405–412; 2001.
54. Helpern JA, Vande Linde AM, Welch KM, et al. Acute elevation and recovery in intracellular magnesium following focal cerebral ischemia. *Neurology.* 1993;43:1577–1581. https://doi.org/10.1212/WNL.43.8.1577
55. Mousain-Bosc M, Roche M, Polge A, Pradal-Prat D, Rapin J, Bali JP. Improvement of neurobehavioral disorders in children supplemented with magnesium-vitamin B6. *Magnes Res.* 2006;19(1):46–52. https://www.ncbi.nlm.nih.gov/pubmed/16846100
56. Secades JJ. GAMALATE B6. Review of a GABAergic product. *J Neurol Neurosurg.* 2017;6(5):1–13. https://doi.org/10.19080/OAJNN.2017.06.555696

57. López-Pousa S, Lombardí C, Ortega E, Novell R. Eficacia de un fármaco GABAérgico (Gamalate-B6) sobre la calidad de vida de los enfermos con fibromialgia. *Psiquis*. 2002;23:31–38.
58. Zamora A, Pérez LM. El bromhidrato de glutamato de magnesio y GABA como tratamiento de la ansiedad. 1990;11:5–8.
59. Martinez M. Gamalate B6 (G-B6) en la ansiedad. *Phronesis*. 1992;13:33-38.
60. Nuñez D, López-Posa S. Cefaleas tensionales. Respuesta a la medicación con Gamalate B6. *Phronesis*. 1991;12:1-4.
61. Espadaler Medina JM, Pujol J, Balcells M, Jubert-Gruart J. Clinical experience with a new medicamental association GB6 in neurologic practice. *Münchener Medizínische Wochenschrift*. 1966;1:3-11.
62. FolchCamarasa L, Folch L, Folch J. Experiencia realizada con GB6 para determinar su influencia sobre los automatismos del pensamiento en discapacitados mentales. *Rapports de Psicologia y Psiquiatria Pediátricas*. 1968;10:1–6.
63. Knobel M. Clinical experience with Gamalate B6 in some infantile mental deficiencies. 1972 (Unpublished data).
64. Vendrell J, Amorós MC, Vendrell DP. Aproximación a un estudio de la evolución de los trastornos del lenguaje en el niño, al combinar la terapéutica logoterápica con una asociación medicamentosa (GB6). *N Engl J Med.* (Spanish Edition). 1973;7(82):51–61.
65. Espadaler JM. Nuestra experiencia en el tratamiento de las disfunciones cerebales mínimas con GB6. *Med. Klin.* (Spanish Edition). 1982;249:39–44.
66. Foch Soler J. El Gamalate B6 en paidopsiquiatría. *Med Klin.* (Spanish Edition). 1983;254:29–36.
67. Martínez M, Alvarado M, Tagle I, Orrillo, E. Gabaergic precursors and neurological learning disorders comparative study of school children in urban-marginal areas of metropolitan Lima. *Revista de Neuropsiquiatria*. 1991;54:113–120.
68. Novell R, Aguas S, Franco M, et al. Tratamiento de los trastornos conductuales en niños con retraso mental ligero y moderado: Eficacia y seguridad de Gamalate B6. *Psiquis*. 1998;7:265–273.
69. Lord C, Risi S, Lambrecht L, et al. The autism diagnostic observation schedule—generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord*. 2000;30(3):205–223. https://www.ncbi.nlm.nih.gov/pubmed/11055457
70. International Ethical Guidelines for Health-related Research Involving Humans. CIOMS/WHO. 2016. https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf. Accessed December 12, 2019.
71. Declaration of Helsinki. World Medical Association, Seoul, 2008. https://www.wma.net/. Accessed December 12, 2019.
72. Law 14/2007 on Biomedical Research (BOE nº 159), dated July 4, 2007 https://www.boe.es/buscar/doc.php?id=BOE-A-2007-12945. Accessed December 12, 2019.
73. Aman M, Singh N, Stewart A, Field C. The Aberrant Behavior rating scale for assessment of treatment effects. *Am J Ment Defic*. 1985;89(5):485–491. https://www.ncbi.nlm.nih.gov/pubmed/3993694
74. Guy W, ed. The Clinical Global Impressions Scale. ECDU Assessment Manual for Psychopharmacology. Rockville: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration; 1976.
75. Harrison PL, Oakland T. Adaptive behavior assessment system. 2nd ed. San Antonio, TX: Harcourt Assessment; 2003.
76. Kaufman A, Kaufman N. Kaufman Brief Intelligence Test. 2nd ed. (K-BIT II). Circle Pines, MN: American Guidance Service, Inc.; 2004.
77. Conners K, MHS Staff. Conners' Kiddie continuous performance test CPT (K-CPT V.5). North Tonawanda, NY: Multi-Health Systems; 2012.
78. D'Elia L, Satz P, Uchiyama C, White T. Color Trails Test. Professional manual, Psychological Assessment Resources, Odessa, FL; 1996.
79. Wechsler D. Wechsler Intelligence for Adults (WAIS IV). Madrid: TEA Ediciones; 1997.
80. Randolph C, Tierney M, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol*. 1998;20(3):310–319. https://doi.org/10.1076/jcen.20.3.310.823
81. Tiffin J. Purdue Pegboard examiner manual. Chicago, IL: Science Research Associates; 1968.
82. Culbertson WC, Zillmer EA. Tower of London-Drexel University. 2nd ed. (TOL^{DXtm}). North Tonawanda, NY: Multi-Health Systems; 2001.
83. García-Alba J, Esteba-Castillo S, Castellanos López MA, et al. Validation and normalization of the tower of London-Drexel University Test 2nd edition in an adult population with intellectual disability. *Span J Psychol*. 2017;20:E32. https://doi.org/10.1017/sjp.2017.30
84. Tirapu-Ustárroz J, Muñoz-Céspedes J, Pelegrín-Valero C, Albéniz-Ferreras A. A proposal for a protocol for use in the evaluation of the executive functions. *Revista de Neurología*. 2005;41(3):177–186. https://www.ncbi.nlm.nih.gov/pubmed/16047302
85. Gioia G, Isquith P, Guy S, Kenworthy L. Behavior rating inventory of executive function. *Child Neuropsychol*. 2000;6:235–238. https://doi.org/10.1076/chin.6.3.235.3152
86. Hassiotis A, Robotham D, Canagasabey A, et al. Randomized, single-blind, controlled trial of a specialist behavior therapy team for challenging behavior in adults with intellectual disabilities. *Am J Psychiatry*. 2009;166:1278–1285. https://doi.org/10.1176/appi.ajp.2009.08111747
87. Welsh MC, Pennington BF, Grossier DB. A normative developmental study of executive function: a window on prefrontal function in children. *Dev Neuropsychol*. 1991;7:131–149. https://doi.org/10.1080/87565649109540483
88. Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. *Biol Psychiatry*. 2005;57(11):1336–1346. https://doi.org/10.1016/j.biopsych.2005.02.006