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Effectiveness of adjunctive therapy with tiagabine in mentally disabled patients with epilepsy

Tiagabine is a potent new antiepileptic drug (AED) which inhibits GAT – the uptake carrier of gamma-aminobutyric acid (GABA) in neuronal and astrocytic cells. The resultant increase in synaptic GABA is thought to account for the compound's anticonvulsant activity (16). Tiagabine has been demonstrated to be effective and well tolerated as adjunctive treatment in adults with refractory partial seizures and in some cases as monotherapy treatment, also in newly diagnosed epilepsy (8, 9). Like other drugs that act on the central nervous system tiagabine has the potential to affect higher cerebral functions. Several studies have found no evidence of psychomotor and cognitive impairment with tiagabine although CNS-related adverse events like a somnolence, difficult concentration, confusion, depressed mood or even psychotic reactions have been reported more frequently than with placebo (9). These impacts of tiagabine are possible to be different in mentally disabled patients with epilepsy. The prevalence of epilepsy is estimated to be about 20-fold higher in people with mental retardation and about 50-fold higher in these with both mental retardation and other motor or behavioural disabilities. Seizures in these subpopulations may be difficult to control and more often require polytherapy (7). The potential benefits of new generation AEDs have not been well studied in these patients, mainly because they are excluded from standard clinical trials. Tiagabine with its precise mechanism of action, minimal drug interaction and no evidence of cognitive impairment seems to be useful but like others has not been specifically studied in developmentally disabled patients with epilepsy.

OBJECTIVE

We tried to determine the efficacy and tolerability of tiagabine (Gabitril ®) as add-on therapy in selected group of young adult outpatients with refractory epilepsy and concomitant mental retardation.

MATERIAL AND METHODS

Study design: prospective, observational, open, non-comparative, short-term – 24 weeks, add-on treatment with tiagabine (TGB) in refractory partial seizures.

Patients: a group of 33 outpatients (18 males, 12 females), mean age: 32.6 + 11.2 years (range: 16-42) with confident diagnosis of both epilepsy (in accordance with ILAE classification) and mental retardation was included in the study. The main inclusion criteria were epilepsy with refractory partial seizures (PS) (simple or complex) without/with 2° generalisation, lasting above 1 year and with a minimum of 4 PS per 4 weeks during last 3 months, an intake of a maximum of 3 concomitant AEDs, and the ability of registering all seizures by a patient himself or care giver in a patient's diary throughout the trial.

Treatment sequence consisted of: baseline observational period – no TGB (weeks (-) 12 to 0, titration – TGB built individually from dose 5 to 70 mg/day (weeks 1 to 8) and maintenance period – constant doses of TGB (range 35-70 mg/day) for individual patients (weeks 9 to 24).

Effectiveness of treatment was estimated by comparing: Efficacy – on the base of: response rate (percentage of responders – patients with > 50% reduction in seizure frequency), mean seizure frequency/month, days with seizures/month and seizure severity (five characteristics of seizures: duration, unconsciousness, time to recovery, injuries, and overall intensity were scored on a 5-point scale ranging from 1 – least severe to 5 – most severe); – percentage of patients with at least one treatment emergent adverse event, laboratory values (standard haematology, clinical biochemistry: liver tests, electrolytes, glycaemia, urea, creatine); Quality of life (QOL). The Quality of Life in Epilepsy-31 Inventory (QOLIE-31) was used for assessment of patients' self-estimation of well-being. Changes in scores in seven subscales of a questionnaire (cognitive function, fatigue/energy, emotional well-being, seizure worry, social functioning, medication effects, overall QOL) were compared between baseline and add-on phase for responders and non-responders.

Statistics. Difference from baseline in test response was compared at 12 and/or 24 weeks of add-on phase using the Wilcoxon test.

RESULTS

Analysis included data from 30 patients (33 at the beginning) who have finished 24 weeks (8 weeks' titration +16 weeks' maintenance) of TGB add-on therapy; 3 persons with profound mental disability were excluded due to protocol violation (Tab. 1). Comparisons were conducted between baseline and 12/24-weeks' treatment period.

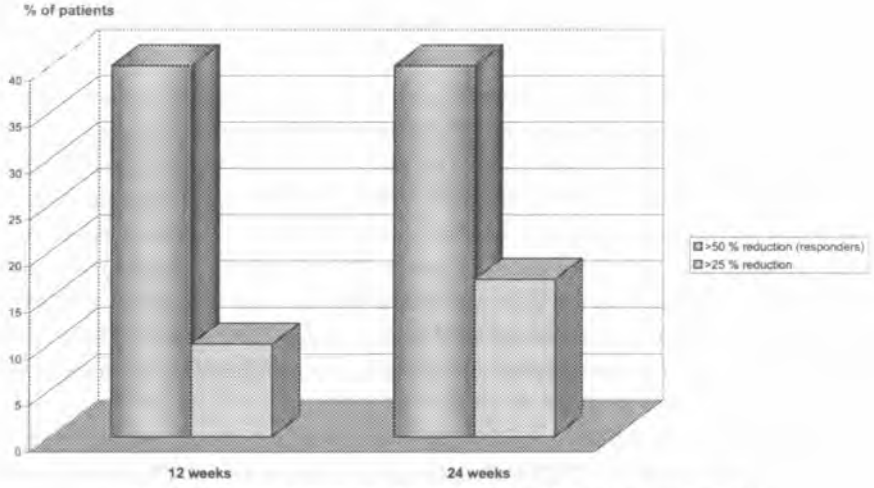

Fig. 1. Seizure reduction during tiagabine add-on treatment

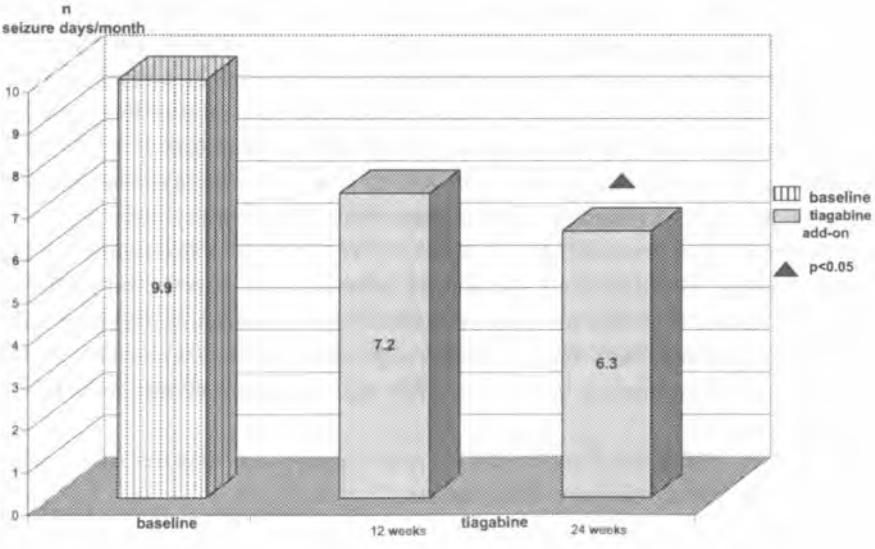

Fig. 2. Seizure – day requancy

Efficacy. About 40% of patients responded to treatment and in another 10% or 17% any perceived improvement was observed respectively after 12 and 24 weeks of treatment although none of the patients became completely seizure free. The effect noted after 12 weeks, that covered 8 weeks' titration persisted at the end of 24 weeks of maintenance phase. There were no cases of increased seizure frequency at follow-up (Fig. 1). Mean number of days with seizures decreased from 9.9 per month at the baseline to 7.2

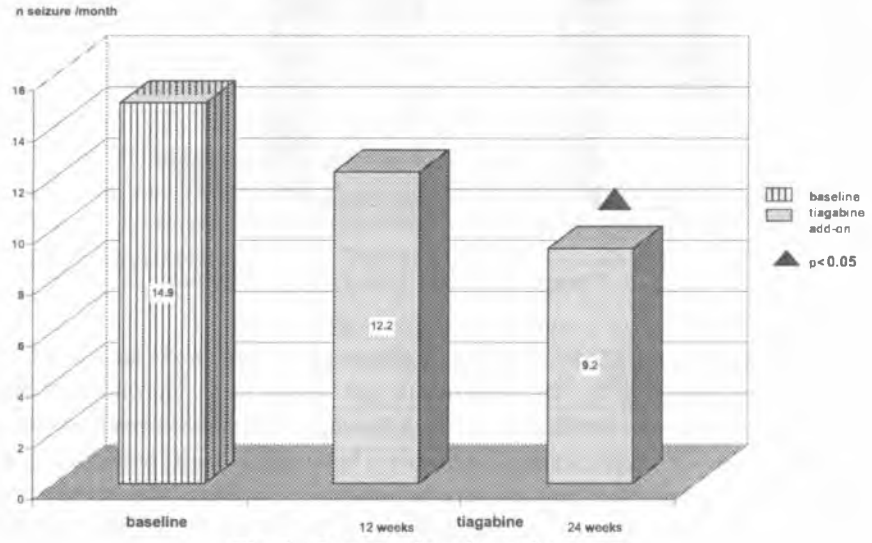

Fig. 3. Decrease in seizure frequency

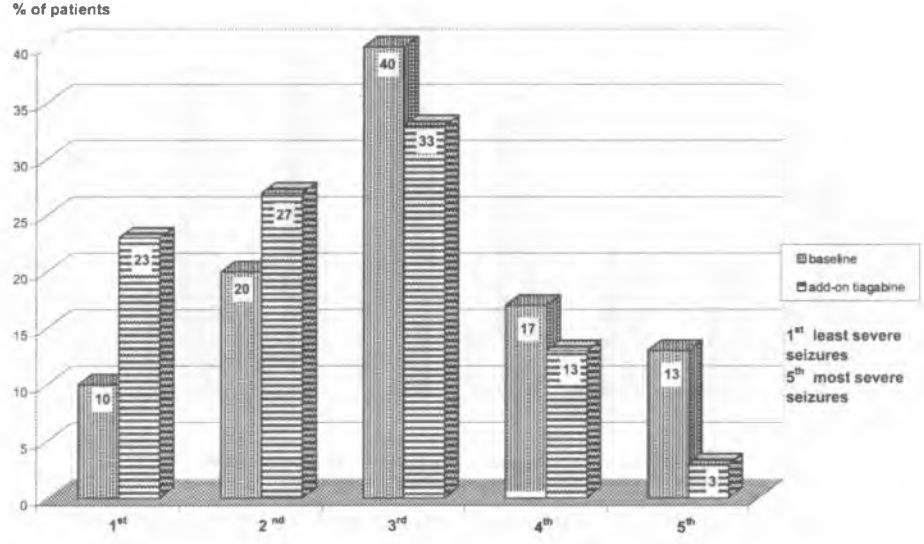

Fig. 4. Overall seizure severity

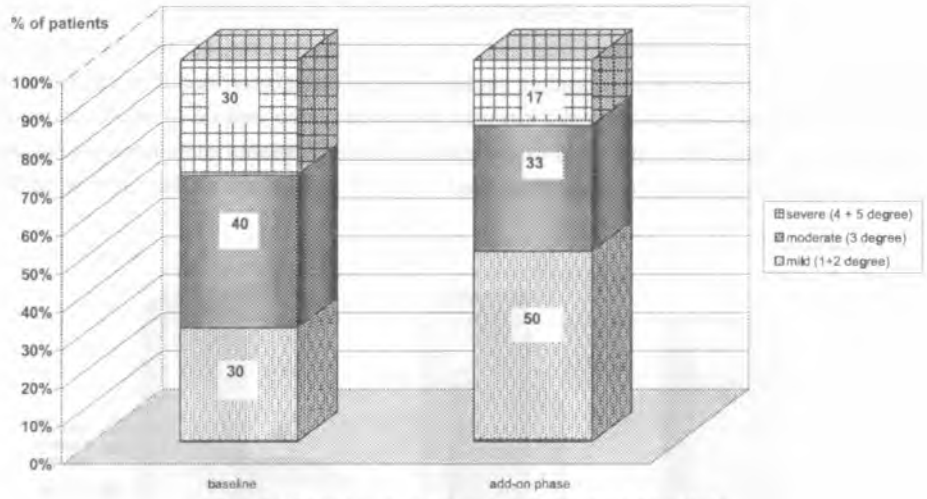

Fig. 5. Change in seizure severity after tiagabine

and 6.3 respectively after 12 and 24 weeks of add-on phase that means above 30% reduction in seizures days (Fig. 2). The seizure rate per month in an individual patient was reduced from 14.9 at the baseline to 9.2 at follow-up (38% reduction in monthly rate) (Fig. 3). At follow-up seizure severity ratings were better for at least three from total five of seizure characteristics, i.e. duration, time to recovery, overall intensity but not for injuries and unconsciousness when compared with baseline. This distinct shift toward im-

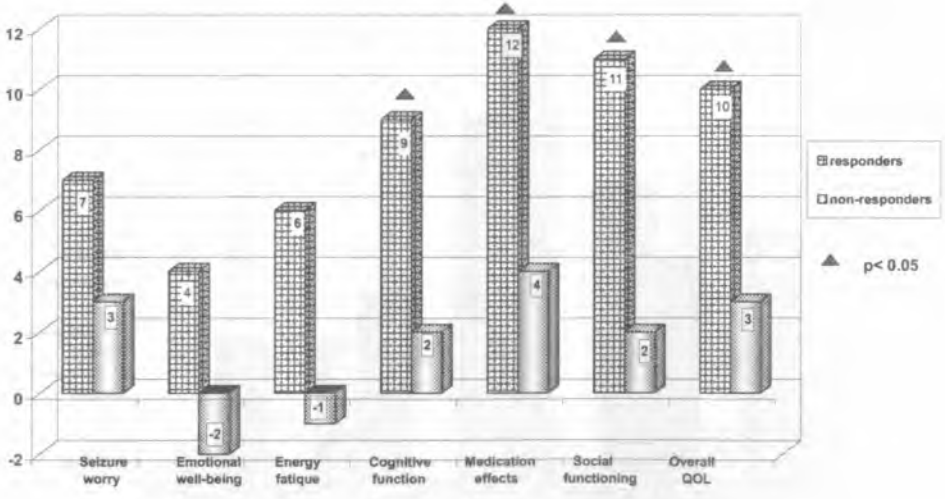

Fig. 6. Change in QOLIE-31 subscales scores at week 24 for responders and non--responders

provement resulted in an increase in mild fits from 30 to 50% of all patients (1st and 2nd degree) and decrease in severe fits – from 30 to 17 % of patients (4th and 5th degree) (Fig. 4, 5).

Tolerability. The majority of patients (90%) did not report any additional adverse events during add-on phase. Another 10% (n=3) reported a total of 12 of them. The most common were complains associated with nervous system (vertigo – in 3 patients, weakness – 3, nervousness – 2, somnolence – 2, headache – 1, concentration difficulty – 1). They did not cause the withdrawal of TGB as well as disappeared spontaneously (n-1) or when the dosing was divided into three portions per day (n-2). Laboratory values did not show any clinically relevant changes in blood count profiles and liver function tests.

Quality of life. Among responders to addiction of TGB to previous AEDs an improvement in most health-related quality of life domains of QOLIE-31 questionnaire was assessed but statistically significant differences as compared with non-responders concerned cognitive function, medication effects, social functioning and overall QOL.

Table 1. Demographics

Gender: male – n (%)	18 (60)
Age (y) – Mean (SD)	32.6 (11.4)
Epilepsy duration (y) – Mean (SD)	19.2 (8.4)
Mental retardation: n (%) mild (50<IQ<70) moderate (20<IQ<50) *(profound (IQ<20)*	24 (80) 6 (20) *(3–excluded from analysis)*
Mental retardation + other cerebral disability–n (%)	8 (27)
Education (years in school) – Mean (SD)	9.8 (2.9)
Seizure type: n (%) SP only CP only 2° generalized only mixed	3 (10) 12 (40) 10 (33) 5 (17)
Baseline seizure rate/month : Mean (SD) (range)	14.9 (5.4) (5-29)
TGB maintenance dose (mg/day): Mean (SD)	48.7 (10.4)

DISCUSSION

The initial data in our study in mild and moderate mentally retarded young adult epileptics with previous pharmacoresistance against partial and secondarily generalized seizures suggest efficacy of TGB similar to that reported in other studies in matched patients without intellectual disability. 55 of patients were treated for 6 months, and only 3 were withdrawn from the analysis because of non-violent protocol. 12 (40%) of analyzed had more than 50% reduction in the frequency of seizures after 3 months' management as compared with baseline rates and such an efficacy persisted after next 3 months. Another 3 (10%) to 5 patients (17%) experienced above 25% reduction in seizure frequency after 3 or 6 months that means no attenuation of treatment activity. As descriptive and non-controlled study, because of difficulties with collecting representative size of this special epilepsy subpopulation within a single center it ought to be considered as qualitative estimation that shows positive influence of TGB addiction in mentally disabled epileptics who did not achieve satisfactory improvement during standard treatment. There was comparable efficacy from 27 to up to 55% of responder rates and 2 or 3-fold better results in comparison to placebo reported in some earlier clinical trials with TBG even if they were conducted according to different study protocols (4). In Ben-Menachem analysis of five multicenter studies performed in about 2,000 patients aged 12-77 years with partial epilepsy with or without generalization, TGB when added to one up to three previous AEDs resulted in about 23% of responders, that means 2.5-fold improvement as positive results were also achieved in 9% of placebo-controls. In this evaluation significant 25% reduction in seizure frequency as well as 6% increase in seizure-free days were noted in comparison to placebo (3).

In our observation better results of treatment were achieved with higher doses of TGB up to 70 mg/day in few patients. It was also pointed out in previous works that higher dosing of TGB during maintenance, even above 70 mg/day in polytherapy resulted in better efficacy (3, 4). On the other hand, this may confirm true pharmacoresistance, that only more "aggressive" management may provide any improvement. Simultaneously it is obvious with all AEDs that higher doses are in a strict relation with more frequent adverse event and toxicity. In our study only 3 of total 30 patients experienced symptoms of poor tolerance and it was indeed with patients who needed the highest dose of 70 mg/day during maintenance. However, complains were reported earlier, during titration, when doses were escalated weekly by 10 mg/day; in all cases side-effects resolved during titration when change in dosing to three times daily was recommended. The patients reported non-specific symptoms of neurotoxicity, that are also known for other AEDs such as vertigo, weakness, nervousness, somnolence, headache or difficult concentration. All of them were transient and none of patients was withdrawn from the investigation because of side-effects. None of the patients in our study and especially affected by side-effects revealed any clinically significant changes in biochemical testing. Similar complains and their resolution were reported also for patients without mental disability in

previous works with TGB both in short-term and prolonged mono- or polytherapy trials (2, 3, 11, 12). Generally, during clinical observations TGB has been shown to be safe and well-tolerated; most frequently reported adverse-effects were CNS related somnolence, dizziness, asthenia, nervousness, depressed mood and emotional liability. They seem to be related to the peak concentration of TBG. In Leppik placebo-controlled polytherapy observation as much as 90% of patients experienced one or more mild, transient and dose-related adverse effects with TGB (12). On the other hand, no idiosyncratic reaction, no abnormalities in haematology or common chemistry values have so far been linked to the use of TGB. It ought to be stressed that TBG is safe when added to any AEDs as it does not cause significant drug interaction and is not associated with an increased risk of any potential side effects of other anticonvulsants (10–13). Adverse effect profile of TGB seems to be especially useful in patients with mental disability for whom it is particularly important that antiepileptic treatment does not cause any deterioration in cognitive functioning. To date no adverse effects on cognitive abilities have been found when neuropsychological effects of TGB add-on and monotherapy were evaluated. In Kalviainen et al. long-term study TGB did not cause deterioration in neuropsychological evaluation and cognitive performance at the doses ranging from 30 to 80 mg/day (8). Also in 3months' add-on treatment of partial seizures TBG at the dose of 30 mg/d showed no changes in various cognitive areas, behaviour and mood (14). Dodrill et al. showed no cognitive effects in monotherapy with TGB in low doses but some evidence for mood effects in add-on treatment with TGB at higher dosing of 56 mg/d, possibly related to titration speed, but reversible when polytherapy was converted to monotherapy (5, 6). In Aikia et al. observation medium doses of TGB did not deteriorate memory, concentration, reactivity speed and even improved cognition during 6 to 24 months' treatment (1). TGB monotherapy seemed to be associated with improvement in psychomotor activity and to cause less fatigue compared with standard AEDs. Simultaneously it was stated that the frequency of TGB-provoked psychiatric disturbances in epileptics with previous psychiatric history was comparable with placebo and tolerance of drug in this special group was the same as in patients without psychiatric dysfunction (9, 15). None of our patients had the past history of psychoses or serious emotional problems and some behavioral disturbances observed earlier in 6 (20%) did not intensify during TGB add-on. Cognitive abilities were not the separate goal of recent observation. However, they were taken into account during assessment of patient sense of the impact of TGB addiction on well-being by the use of quality of life questionnaire (QOLIE 31). There were positive findings in most of total seven subscales of questionnaire domains in patients who responded to antiseizure activity of TGB added to previous therapy. Significant improvement was reported according to cognitive functions, medication effects, social functioning as well as overall quality of life; these subscales improved over twice or three times as much as for non-responders. Marked improvement was seen in enhanced patients perception of concentration, memory and language that are three aspects of cognition.

Observation of these changes in the range of 9 to 12% indicates that the patients perceived marked enhancement attributable to TGB when added to previous medication.

Although our investigations suggest that TGB improves clinical state and health related quality of life in patients with drug resistant epilepsy and intellectual disability the small size of trial and lack of control reduce the utility of the results. The continuation of this initial observation is needed in larger and controlled studies.

CONCLUSIONS

1. 40% of mentally disabled patients responded to short-term add-on treatment with tiagabine.
2. The number of monthly seizure-days and mean seizure frequency decreased by above 30% over the baseline.
3. Significant proportion of patients experienced improvement in seizure severity.
4. Add-on therapy with tiagabine was well-tolerated in terms of patient well-being and clinical laboratory tests.
5. The positive impact of polytherapy with tiagabine on health-related quality of life was more particularly observed among responder patients.

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SUMMARY

Previous reports justified positive impact of tiagabine, a new-generation antiepileptic drug on neuropsychological functioning as well as minimal risk of psychiatric exacerbations. In this prospective, open, observational, non-comparative, short-term – 6 months' study we evaluated efficacy and tolerability of tiagabine as add-on in polytherapy in 30 young adults with both refractory epilepsy and mild or moderate mental retardation. About 40% of patients experienced improvement in seizure frequency of 50% or more and none complained of seizure deterioration. Overall seizure frequency fell down from a mean 9.9 at the baseline to 6.3 seizure days per month. The seizure rate was reduced from 14.9 to 9.2 per month after 24 weeks of add-on phase. Adjunctive tiagabine therapy appeared to be associated with reduction in overall seizure severity characteristics expressed as enhancement of mild seizures from 30 to 50% of patients and reduction in severe seizures from 30 to 16%. Responders reported an improvement in most health-related quality of life domains but mostly cognition, medication effects and social functioning. The majority (90%) of patients did not report additional adverse effects with tiagabine; the most common complains associated with central nervous system (vertigo, weakness, nervousness) were transient and did not cause discontinuation. Blood counts and liver functional tests did not show any clinically relevant changes. In this short-term observation tiagabine seemed to be a beneficial antiepileptic drug for mentally retarded

patients with epilepsy as it decreased seizure frequency and severity, improved the patients' sense of the quality of life without enhancement of the risk of adverse effects in polytherapy.

Efektywność tiagabiny w politerapii w padaczce u pacjentów z dysfunkcją intelektualną

W licznych badaniach, poza skutecznością, pokreślano korzystny wpływ tiagabiny, leku przeciwpadaczkowego nowej generacji, na funkcjonowanie neuropsychiczne pacjentów z padaczką jak również minimalne ryzyko wystąpienia niepożądanych zaburzeń psychicznych. W obecnym prospektywnym, niekontrolowanym placebo, krótkoterminowym 6-miesięcznym badaniu oceniono skuteczność i tolerancję stosowania tiagabiny jako leku dodanego w grupie 30 młodych dorosłych pacjentów z padaczką lekooporną oraz współistniejącym upośledzeniem umysłowym w stopniu lekkim lub umiarkowanym. U 40% leczonych stwierdzono przynajmniej 50% redukcję częstości napadów (responderzy), liczba dni z napadami zmniejszyła się z 9,9 do 6,3 na miesiąc, a średnia częstość napadów uległa zmniejszeniu z 14,9 do 9,2 na miesiąc. Odnotowano także złagodzenie ciężkości napadów: odsetek pacjentów z napadami umiarkowanymi zwiększył się z 30% przed stosowaniem tiagabiny do 50% po 24 tygodniach terapii, a odsetek chorych z napadami ciężkimi zmniejszył się odpowiednio z 30 do 16%. U pacjentów-responderów w badaniu kwestionariuszem jakości życia stwierdzano poprawę wszystkich ocenianych funkcji, ale najwyraźniej funkcji poznawczych, korzystną ocenę wpływu leczenia na ogólne samopoczucie oraz poprawę w funkcjonowaniu społecznym. Większość pacjentów (90%) nie doświadczyła istotnych objawów niepożądanych leczenia; najczęstsze skargi wiązały się z łagodnymi, przemijającymi efektami neurotoksycznymi (zawroty głowy, astenia, rozdrażnienie), które nie stanowiły powodu odstąpienia od próby. Nie odnotowano zaburzeń aktywności psychofizycznej, zachowania, nastroju. Nie stwierdzono również istotnych odchyleń od normy w klinicznych badaniach biochemicznych. Przeprowadzona obserwacja pozwala sądzić, że tiagabina może być odpowiednim lekiem przeciwpadaczkowym również w padaczce u chorych z deficytem intelektualnym, bowiem wyraźnie wpływa na redukcję zaburzeń napadowych, bez powodowania objawów niepożądanych, w tym zaburzeń w sferze funkcjonowania neuropsychicznego, oraz zapewnia poczucie poprawy jakości życia w chorobie.