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DOUBLE EFFECT OF PREGABALIN ON ANXIETY AND DYSLIPIDEMIA

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INTRODUCTION

Pregabalin (PGB) is an approved medication for the treatment of epilepsy, neuropathic pain, and generalized anxiety disorder. It is a structural analog of the inhibitory neurotransmitter amino butyric acid (GABA). It suppresses excitatory neuronal transmission via 2-ligands in voltage-sensitive calcium channels, although the exact mechanism is unknown. It also inhibits the release of neurotransmitters like glutamate, noradrenaline, and substance P. The use of 150–600 mg/day in Turkey as an adjunctive treatment for fibromyalgia, generalized anxiety disorder, and adult patients with partial epilepsy has been approved by the Ministry of Health.

Pregabalin's most common side effects ,when used at therapy levels, are weight gain, peripheral edema, dizziness, and face rash. The frequent side effects of dizziness and somnolence, are typical causes for stopping pregabalin treatment (Stahl 2021).

We hypothesized that we could better understand the mechanism of action of pregabalin through the side effects, some of which seem contradictory e.g.weight gain and improvement in dyslipidemia.

Here, we presented a patient with a diagnosis of a generalized anxiety disorder who had a positive change in dyslipidemia after starting pregabalin with follow-up.

CASE REPORT

A 52-year-old male patient was admitted to our outpatient clinic with complaints of feeling depressed, being on his toes all the time, fatigue, irritability, restlessness, and constant worry that something bad will happen. Although these complaints have been present for about 15 years and have ameliorated from time to time, the patient did not have a history of complete recovery, visited many centers and saw many doctors.

He used nearly all the drugs used for the treatment of anxiety including paroxetine, clomipramine, trazodone, mirtazapine, lamotrigine, duloxetine, oxcarbazepine, fluoxetine, olanzapine, aripiprazole, mianserin, escitalopram, reboxetine, sulpiride, medazepam, trifluoperazine, vortioxetine, clonazepam, diazepam.

He received 8 sessions of electroconvulsive therapy and 40 sessions of transcranial magnetic stimulation during major depressive episodes comorbid with generalized anxiety disorder. A pharmacogenetics analysis report made in a research center 4 years ago, revealed that he was sensitive to lamotrigine. After using it for a while, this treatment was discontinued because there was not enough benefit.

The pharmacologic treatment of the patient at the time of admission was duloxetine 60 mg/day, paroxetine 20 mg/day, and quetiapine 100 mg/day. He had a diagnosis of diabetes mellitus type 2 for 5 years which was well controlled with metformin 1000 mg/day.

The patient was hospitalized with treatment-resistant generalized anxiety disorder. After reviewing previous treatments, we decided to switch to pregabalin.

In the blood tests performed on the first day of the hospital stay; total cholesterol was 252 mg/dL, triglyceride 257 mg/dL, HDL 30 mg/dL, and LDL 160 mg/dL, while other results were within the normal range. In the blood tests repeated 14 days after the patient was started on pregabalin 150 mg/day, total cholesterol was 193 mg/dL, triglyceride was 154 mg/dL, HDL was 35 mg/dL, and LDL value was 122 mg/dL. The blood sample was taken from the patient at 07.30 in the morning while the patient was fasting before the blood draw.

During this period, the patient did not receive any additional treatment that would affect his metabolic status. His current metformin treatment was continued. No medication was started or stopped with pregabalin. There was no use of any statins or fenofibrates. And there were no known drug interactions between pregabalin and metformin. The Beck Anxiety Scale score, which was 38

Table 1 After pregabalin treatment dyslipidemia changes.

	Total Cholesterol	Triglyceride	LDL	HDL
Before 150 mg/day Pregabalin	252 mg/dL	257 mg/dL	160 mg/dL	30 mg/dL
After 150 mg/day Pregabalin	193 mg/dL	154 mg/dL	122 mg/dL	35 mg/dL

at the time of admission, decreased to 7 at the time of discharge. After 17 days of hospitalization, he was discharged with Pregabalin 150 mg/day, Duloxetine 30 mg/day, and Quetiapine 100 mg/day in almost complete remission (Table 1). There was no change in the patient's diet during the treatment process.

The improvement in dyslipidemia after switching to pregabalin in our patient, whom we followed up with the diagnosis of "generalized anxiety disorder", drew our attention. Patient consent was obtained for this case report.

DISCUSSION

A structural analog of the inhibitory neurotransmitter GABA, which functions as an inhibitory neurotransmitter in the human brain, is pregabalin [(S)-3-(aminomethyl)-5-methylhexanoic acid]. It is prescribed for conditions like fibromyalgia, generalized anxiety disorder, partial epileptic seizures, and neuropathic pain. Pregabalin was initially created as an antiepileptic drug (Stahl 2021). It is thought to work by binding to the voltage-gated calcium channel's -2-subunit in overexcited presynaptic neurons in a state-dependent manner, inhibiting the release of excitatory neurotransmitters like glutamate and substance P and boosting GABA levels in a variety of brain regions, including the neocortex, amygdala, and hippocampus (Li et al. 2011). It lessens the central nervous system's release of excitatory neurotransmitters. Pregabalin lowers the levels of several neurotransmitters, including substance P, glutamate, dopamine, and noradrenaline. It does not bind to GABA receptors despite the name (McKeage and Keam 2009).

Pregabalin's exact mechanisms of action are unknown. Pregabalin is a Gamma Amino Butyric Acid lipophilic analog (GABA). Peak plasma concentrations of PGB are reached after 1 hour of fast absorption. PGB has linear (first-order) kinetics, which causes the serum concentration to rise proportionately to the dosage. PGB is not protein-bound, has a narrow volume of distribution, a high water solubility, and a low lipophilicity (Bockbrader et al. 2010).

Dizziness, vertigo, instability, ataxia, diplopia, blurred vision, tremor, sleepiness, confusion, loss of focus, euphoria, disordered thinking, weariness, facial rash, peripheral edema, and weight gain are the most frequent adverse effects of pregabalin (Zaccara et al. 2011).

It is known that stress affects on lipid metabolism. Stress, especially associated with major disasters, has been shown to increase blood triglyceride, LDL and total cholesterol levels. One of the leading mechanisms here is that it affects the cortisol level on the HPA axis (Veen et al. 2009). However, there are studies in the literature suggesting that anxiety symptoms are associated with low HDL levels and abdominal obesity (van Reedt et al. 2013). It can be thought that the decrease in the level of anxiety in the case caused an improvement in biochemical parameters since it affected the related hormonal axes such as glucocorticoids.

In addition, there are cases of hypertriglyceridemia reported to be associated with pregabalin in the literature. In a case whose TG value was found to be 452 mg/dL after starting PGB 600 mg/day, it was observed that the triglyceride level returned to the normal range after switching to gabapentin. This change was attributed to the different pharmacodynamic effects and bioavailability of gabapentin (Bonnet et al. 2014).

In this case, the causality between pregabalin and changes in dyslipidemia was assessed with Naranjo Adverse Drug Reaction Probability Scale (Naranjo et al. 1981). There is some evidence in the literature showing that pregabalin affects dyslipidemia (Abou Zeid et al. 2017; Parsons and Emir 2017)(1 point). Scoring could not be done for the related items(3,4, and 6-10) of Naranjo ADRS because there was no specific antagonist, discontinuation of the drug, placebo control, level determination in body fluids, or any objective evidence (0 points). Changes in dyslipidemia appeared 14 days after the administration of medication (2 points). There were no likely factors to cause this reaction other than the drug (2 points). The total score of our case was 5 points which means 'probable'. When evaluated according to Naranjo ADRS, it was thought that the related side effect might be related to pregabalin treatment.

It is known that antiepileptics have unfavorable effects on liver and lipoprotein mechanisms. However, it is also known that pregabalin is metabolized in the liver to a negligible level (Boomershine 2010). Antiepileptic

drugs can affect serum lipid concentration when used for a long time. It has been suggested that microsomal enzyme-inducing drugs such as phenytoin and carbamazepine may affect serum lipid and apoprotein concentrations (Brämswig et al. 2002). However, although there is no such feature of pregabalin, it is interesting to observe the current effect after such a short use.

The pharmacokinetic mechanism of hypertriglyceridemia is unlikely because pregabalin does not bind to plasma proteins and is not metabolized by or inhibited by hepatic enzymes. Pregabalin has a greater inhibitory effect on voltage-gated calcium channels containing the alpha2-delta-1 subunits. However, a link between these calcium channels and lipid transport, synthesis, or metabolism could not be found in the literature (Bockbrader et al. 2010).

Since the changes in pregabalin dose and metabolic values were not followed after discharge, it is difficult to discover a continuous relationship. Follow-up studies can be conducted on this subject. Another point is the current effect of pregabalin may have originated from genetic variations.

CONCLUSION

A favorable effect of pregabalin use in generalized anxiety disorder is the improvement of metabolic parameters especially related to lipid metabolism, along with the alleviation of severe anxiety symptoms. Since the majority of psychotropics have negative effects in this sense, the mentioned positive effect of PGB is valuable in terms of preferability. It can be concluded that preferring pregabalin instead of atypical antipsychotics or benzodiazepines as an adjunct treatment in patients with generalized anxiety disorder comorbid with dyslipidemia may provide additional benefits to the patient.

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