

## A CASE REPORT WITH A MINI-REVIEW OF THE LITERATURE ON THE OVEREATING AND WEIGHT GAIN DUE TO PROPRANOLOL

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### INTRODUCTION

As a non-selective  $\beta$ -blocker propranolol, which is widely used in many branches, is one of the first/most preferred drugs among the treatments for extrapyramidal system side effects such as akathisia and tremor secondary to psychotropic use in psychiatry. Commonly known side effects of  $\beta$ -blockers include bradycardia, hypotension, hypoglycemia, weakness, and feeling of depression, while increased appetite or weight gain are not among the noticeable side effects.

### CASE

A 34-year-old female patient, admitted to our out-patient clinic with complaints of low mood, irritability, anhedonia, reluctance, pessimism, and boredom. She was diagnosed with Depressive Disorder according to DSM V and started fluoxetine 20 mg/day. At control examination on the 20<sup>th</sup> day, she complained of tremor and propranolol 20 mg/day was added to the treatment considering psychotropic induced tremor. After starting propranolol, the patient had an excessive appetite increase in 3 days (she increased from 1 slice of bread to 5 slices of bread for breakfast) and gained 3 kilograms, and ended the propranolol treatment voluntarily. In the physical examination and laboratory tests, no reason was found to explain the weight gain. In the next control examination, the patient whose depressive complaints decreased, but tremor continued, was informed to evaluate the side effects of the drug and after obtaining her consent, propranolol 20 mg/day was restarted. After 50 days of propranolol use, a total weight gain of 4 kilograms especially more pronounced in the first week was recorded. When the "Naranjo Adverse Drug Reaction Probability Scale" was applied, the score was 8 points, thus evaluated as "High Possible Effect".

### DISCUSSION

In the literature review on this subject, there were no publications other than a few old studies and a few

recent case reports. In a double-blind randomized controlled study planned in 1990 to investigate the long-term effect of propranolol on weight in 3837 patients after myocardial infarction, weight gain was found to be higher in the group using propranolol for 40 weeks (2.3 kilograms) compared to the placebo (1.2 kilograms) (Rössner et al. 1990). In 1993, 9 kilograms of weight gain in a patient who used 80 mg/day propranolol for 9 months for migraine prophylaxis was reported as a case report. In a review of 7048 patients, 3205 of whom received  $\beta$ -blocker therapy, the patients were followed for 6 months to 10 years; at the end of the study, in 7 of the 8 evaluations, the body weight was found to be higher in the group using  $\beta$ -blockers compared to the control group (Sharma et al. 2001). In a study comparing the side effects of drugs used in migraine prophylaxis, weight gain (average 6 kilograms) was observed in 8% of the patients who received 80-160 mg/day propranolol after 6th-month of use (Maggioni et al. 2005). In a similar case report in 2015, a 34-year-old female patient complained of tremor secondary to psychotropic use, and 40 mg/day propranolol was added. Her appetite increased in 2 weeks and she gained 3 kilograms and then stopped propranolol deliberately. With the recommendation of her doctor and with her consent, she restarted propranolol and had an excessive increase in her appetite and recurrent weight gain in 1<sup>st</sup> week. Her appetite returned to normal when the drug was stopped (Eslami Shahrabaki et al. 2015). In another case report, a 28-year-old female patient diagnosed with idiopathic ventricular tachycardia without any additional drug-alcohol-substance use was followed up for 12 weeks with 80 mg/day propranolol. The patient who was overweight according to body mass index (BMI: 26.9 kg/m<sup>2</sup>), gained 9 kilograms in the 12-week follow-up due to the increase in appetite and sugar consumption then entered into the obesity limits (BMI: 30.1 kg/m<sup>2</sup>). Previous studies have confirmed that propranolol may participate in lowering blood glucose levels in combination with anti-hyperglycemic treatments such as insulin or metformin, by decreasing Tnf and PKA protein expression, while increasing the expression of Slc2a4

and glucose transporter-4 (GLUT4) (Alves-Wagner et al. 2015). In this case, weight gain was attributed to the mild hypoglycemic side effect of propranolol, as the patient tried to cope with hypoglycemia with sugary foods rather than with a healthy meal (Barrouq & Irshaidat 2020).

Propranolol is a potent lipophilic drug belonging to the class of nonselective  $\beta$ -blockers. It inhibits all three  $\beta$ -adrenergic receptors, with an affinity for  $\beta_1$ - and  $\beta_2$ -receptors 100 times higher than for the  $\beta_3$  receptors (Cannon & Nedergaard 2004). Although it has been used actively for about 60 years, its molecular mechanism has not been fully elucidated yet. The reason for weight gain due to propranolol is attributed to the effects of  $\beta$ -blockers on metabolism, lipid profile, and glucose metabolism. Theoretically, the most frequently accused is  $\beta_3$  receptor antagonism.  $\beta$ -receptors increase fat metabolism via cAMP.  $\beta$ -blockers may also cause weight gain by inhibiting lipolysis in response to adrenergic stimulation.  $\beta_1$ -2 and 3 receptors are expressed in brown adipose tissue. Thermogenesis, the main function of brown adipose tissue, is also responsible for heat production after exposure to cold or large energy intake by diet. Studies have shown that  $\beta_1$ -2-3 receptor knockout mice are susceptible to hypothermia induced by cold or feeding, which leads to cold intolerance and obesity (Ueta et al. 2012).

Another study showed that obese hypertensive patients using  $\beta$ -blockers had a 12% reduction in metabolic rate compared to obese hypertensive patients who received different antihypertensives (Kunz et al. 2000). It was stated that  $\beta$ -blockers reduce the total energy consumption by about 5-10%, which corresponds to 100 to 200 kcal/d per day. That decrease in energy consumption can easily explain the 1 to 3.5 kg weight gain observed in clinical studies. Rather than a steady reduction in energy expenditure causing a sustained weight gain, a reduction in energy expenditure not accompanied by a reduction in energy intake will result in weight gain until the positive energy balance is neutralized by the increased metabolic demand of increased tissue mass (Jéquier & Tappy 1999). This result may explain the observation that weight gain is more pronounced in the early period. Apart from their direct metabolic effects,  $\beta$ -blockers may also adversely affect total energy expenditure by causing fatigue and/or reducing anxiety and so reducing so-called 'fidgeting'.

Weight gain as a rare side effect of propranolol may be due to pharmacokinetic differences. The  $\beta_2$ -adrenergic receptor (ADRB2) is involved in the regulation of energy balance, both in catecholamine-induced lipolysis in muscle tissue and thermogenesis+stimulation of lipid mobilization in adipose tissue. The  $\beta_3$ -adrenergic receptor system is important in the stimulation of lipolysis by catecholamines in white adipose cells and the development of obesity in humans. Various studies have shown that  $\beta$ -adrenergic receptor polymorphisms are associated

with both the risk of developing obesity and a low metabolic rate. It has been shown that the  $\beta_2$ -adreno-receptor Arg16Gly and Gln27Glu variations and the  $\beta_3$ -adrenoreceptor Trp64Arg variation have a significant effect on the future increase in body weight in initially non-obese and normotensive male subjects (Masuo et al. 2005). In addition, since sympathetic and thermogenic responses to food have been shown to decrease with age, the weight gain-inducing effect of  $\beta$ -blockers may be more pronounced in younger individuals than in older individuals (Schwartz et al. 1990).

## CONCLUSION

The mechanism has not yet been fully elucidated by which individual receptor sensitivity differences and weight gain are related, especially in acute short-term use. What is noteworthy in the literature is that although weight and appetite increases are common, they are ignored in side effect studies. However, as seen in the case reports, weight gain is a condition that impairs drug compliance, especially in female patients. Another feature of our case is that weight gain is observed at the lowest propranolol dose, in the shortest time (3 kg in 3 days), faster than previously reported. In the future, the effect of propranolol on weight gain seems to be among the topics that can be investigated through the  $\beta$ -receptor profile and sensitivity differences between the cases.

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### Contribution of individual authors:

Rabia Kevser Boyraz has contributed to the literature search, and writing the draft.

Ebru Şahan contributed to case follow-up, literature research and revision of the manuscript.

İsmet Kırpınar contributed to the supervision of the manuscript.

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