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Review Article

Timolol Eye drop, side effect in the form of Major Depressive Disorder with Psychotic Features

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Abstract

Investigating the drug side effect of timolol eye drops in glaucoma patients is not a new topic, but has been discussed for years, especially the psychological side effects of this drug on patients have been a proven issue. The case, which I am reporting, was a patient who had no psychological problems whatsoever until the age of 62, he had open-angle glaucoma after one year of starting treatment with timolol drops. But despite the fact that he had glaucoma surgery two years ago and his disease has improved to the point where he no longer takes any medication for glaucoma, the question is, why is the patient's depression not improving and I am still faced with ups and downs in his clinical condition, the patient is still being treated with antipsychotic drugs, and this question remains unanswered?

Keywords*: Glaucoma, Side Effects, Timolol, Psychological Problems.*

Introduction

When I noticed in 2022 that one of my old patients was suffering from symptoms such as depression and isolation, it was very hard for me to believe it, as I have worked in this field for more than four decades and have known this patient for more than thirty years. However, when I talked to his family and the patient himself, I talked to him several times about his new problems, which were the first he had encountered, and finally I accepted that he was also suffering from depression. A patient who is basically highly educated, has close relationships with friends and family, is an expert in computer and information matters, is hardworking, has very good relationships with those around him, is innovative, suddenly finds himself in a situation where he is unable to even do his daily tasks and does not talk to anyone. Someone who could previously run an office with a lot of employees would not even be willing to talk to those around him today. He remained in the same position for a long time, in absolute silence, with his eyes fixed on the distance. He had no desire to eat, even though he sometimes only ate one meal a day, and not because he wanted to, but he did not want to eat at all. His sleep was much, much worse, even though he lay in bed for hours, staring at the ceiling, but he did not even blink. Even if he slept, he would wake up again at the slightest sound or movement.

Considering the concerns, he had caused around him, his family asked me to follow up on the matter seriously and help in this way. I wanted to see how I could interpret the cause of this depression and his self-absorption. Although he was an experienced manager in his job, he could not establish friendly or professional relationships even with his old colleagues. In fact, my motivation for investigating this issue came from the fact that, given the comprehensive understanding I had of this patient, I wanted to know why this patient had encountered this problem and how I could help him get out of this situation.

About glaucoma Diseases:

This term refers to a group of eye diseases that damage the optic nerve due to increased pressure inside the eye. Glaucoma can cause serious vision problems, including blindness. Although there are several diseases that can cause glaucoma, most glaucoma is caused by a lack of fluid drainage from the eye.

Known risk factors for glaucoma:

All people over 60 years of age and diabetic patients are at risk for this disease. It is said that this disease is twice as common in diabetic patients and six to eight times more common in African Americans over 40 years of age than in whites.

Types of glaucoma:

•Open-angle glaucoma:

The vast majority of glaucoma cases are open-angle glaucoma. At least 9 out of 10 people with glaucoma have this condition. It is sometimes known as chronic glaucoma or primary glaucoma. About 3 million Americans have open-angle glaucoma.

•Angle-closure glaucoma:

Sometimes the angle between the iris and the cornea is blocked by the iris. This causes angle-closure glaucoma. When the angle is blocked, fluid cannot drain out of the eye as it normally would, leading to eye pressure problems and possible blindness, as with all types of glaucoma. Angle-closure glaucoma tends to be hereditary. About half a million people in the United States have this condition. People of Asian descent and people who are nearsighted are more likely to have it.

•Normal Tension Glaucoma (N.T.G)

It is more common in Japanese people, those with a family history of the condition, and those with an irregular heartbeat or a history of systemic heart disease.

•Congenital glaucoma

Some children are born with glaucoma.

Most children with this condition are diagnosed in their first year of life.

Glaucoma treatment

Other than using topical or oral treatments, requires surgical procedures if the patient is not controlled.

Laser surgery for glaucoma

Laser surgery is often the first step in treating glaucoma before using traditional surgery. Using a highly focused beam of light, a small hole is created in the eye tissue to allow fluid to drain more freely.There are different types of laser surgery for patients with glaucoma, depending on the cause of the disease and its severity.

• Selective Laser Trabeculoplasty (Selective Layzer Terbeloculoplasty)

• Argonne Laser Trabeculoplasty (Argonne Layzer Terbeloculoplasty)

• Laser Peripheral Iridectomy (Layzer Peripheral Iridectomy)

• S Laser Cyclophotocoagulation is Layzeric Cyclophotocoagulation.

In some cases, these facilities are not available to ophthalmologists or they cannot solve their patient's problem with these methods. Then they turn to traditional glaucoma surgery. This type of surgery reduces eye pressure in about 60 to 80 percent of cases and, depending on the effectiveness, may require more surgery.

Background

My patient, a 66-year-old man with a history of hypertension and hyperlipidemia, is under the supervision of various doctors and is controlled. In terms of risk factors, he was a completely suitable person and walked

for an hour every day. In 2019, it was determined during the annual check-up exams that his eye pressure was close to 42. Numerous visits to ophthalmologists finally determined that he was suffering from open-angle glaucoma and, like other patients I know closely, he was started on timolol drops under the supervision of eye specialists. Until 2022, the patient had no neurological or psychological problems. But this year, his friends suddenly noticed that he was secretly avoiding showing himself in limited friendly gatherings and was not willing to be in these gatherings. His sleeping, resting, working, and even eating habits were out of order and he lived a life of chaos. Whenever someone asked him, he said that it was not like that. I want to rest a little or I have worked too much and am tired. He has no desire to have relationships with his employees, whom he has worked with for years. Despite the patient's own wishes, his family brought him to me and I realized very well at the very first visit that his personality had completely changed and that social personality of his years was gone. He did not even tell me, who I had known him for years, what his main complaint was. He only talked to me about his sleep problems. Considering the patient's problem, I took him to my colleague Dr. Eugene Sotiri Psychologist and consulted with him in person about this. The diagnosis was clear that he was suffering from depression and bipolar disorder. Considering the patient's social status and his relationships, which had not changed seriously, we also had to ask ourselves what was the cause of this problem? This posed a great challenge for us and...

Psychological side effects:

We do not want to rule out the psychological side effects of the drug Timolol. These complications have been proven, and this does not mean that this issue may necessarily occur in all patients. Some studies and research have emphasized this issue. When patients stay in the hospital for a long time or are threatened with blindness due to glaucoma, they automatically have complications and fear in their mood and then turn into psychological symptoms.

Reactions to topical timolol, researchers have sought to determine whether topical beta-blockers also have the same risk. For example, topical timolol has been compared to topical Taxol in several studies, and complications when oral timolol was used in patients with blood pressure and heart disease, episodes of neuropsychiatric events have also been identified.

Table 1. Case reporting of neuropsychiatric adverse events from topical timolol

Age	Gender	Event	Topical therapy	Resolution	Complicating features	Past psychiatric history	Year	Reference
71	M	Worsening myasthenia gravis	Timolol	1 day	Chronic myasthenia gravis	No	1979	29
<1	?	Apnea	Timolol	1 day	Bilateral ocular anomalies	No	1979	30
78	F	Syncope, visual hallucinations	Timolol	2 hours	None	No	1980	31
65	F	Depression	Multiple	2 days	Suicidal ideation	No	1982	32
65	M	Impaired response to hypoglycemia, diabetic	Timolol	After cessation	Frequent hypoglycemic episodes	No	1983	33
78	M	Amaurosis fugax, transient ischemic attacks	Timolol	5 days	Arrhythmia	No	1985	34
74	F	Depression	Timolol, Pilocarpine	3 weeks	Bradycardia, taking antipsychotic meds	Yes	1993	35
65	M	Depression, insomnia	Timolol, Acetazolamide	Several days	None	No	1993	36
87	F	Lethargy, insomnia	Timolol	Several days	Bradycardia	No	1997	37
70	M	Depression	Timolol, Travaprost	1 month	Past depression also worsened with other beta-blockers	Yes	2008	38
<1	F	Apnea, hypotonia	Multiple	1 day	Congenital glaucoma, cardiogenic shock, bronchoconstriction	No	2013	39
Four patients (ages 66-93)	All F	Visual hallucinations	Variable	Several hours to days	Some existing neurologic impairment, all had retrial of medication to confirm	No	2017	40

Table of prevalence of psychological diseases in patients who have been treated with timolol eye drops

Of course, in this case, we were faced with these symptoms in a patient whose problems and problems we had comprehensively examined, and even to eliminate metabolic diseases, we had to first rule out various endocrine diseases so that we could later focus on the main disease. The patient first presented with problems such as headaches, weakness, lethargy, excessive loss of appetite, heaviness in the head, sleep disorders, dizziness, and imbalance. We had to first examine and evaluate the metabolic problems that might be causing these symptoms in this patient. When all these examinations were done and we could not reach a specific diagnosis, I discussed the issue of the timolol drug side effect with the ophthalmologists involved, and they raised the issue that could be a side effect of using timolol, otherwise we ourselves had no experience in this regard.

We have had and continue to have more than 300 glaucoma patients in our clinic, and all of these patients have been treated with conventional treatments and their problems have been controlled for years with this condition, and we had no experience with this issue that one of the side effects of using timolol drops could

be bipolar disorders. Later, when I introduced him to my friend Dr. Eugene Sotiri, a psychologist, he agreed with us that the cause of the patient's condition in this case was the timolol side effect.

I cannot be certain whether our case and his psychological side effect were not caused by glaucoma. I emphasized this issue further, based on the experiences of more than 300 male and female patients who had suffered from this disease for years, that this patient had no previous psychological complications and that our patients did not face this problem at all. The reason was clear to us because this patient had lived in very excellent relationships with each other and the challenges that existed in another social environment were generally far from them. However, in other studies, and the fact that glaucoma can cause psychological complications in patients has been significant for us, including

Table 6 Associations of self-reported glaucoma with depression and anxiety in the Gutenberg Health Study (GHS), 2007–2012

	Model 1				Model 2			
	OR	CI	*P*-Value	n	OR	CI	*P*-Value	n
Depression (PHQ-9 ≥ 10)	1.08	0.69–1.62	0.72	14,359	1.10	0.50–2.38	0.80	14,061
Anxiety (GAD-2 ≥ 3)	1.15	0.70–1.78	0.55	14,288	1.48	0.63–3.30	0.35	13,991

PHQ-9 Patient Health Questionnaire, *GAD-2* Generalized Anxiety Disorder Scale, *OR* Odds ratio, *CI* 95% confidence Interval
Model 1: logistic regression analysis adjusted for age, sex, socio-economic status; Model 2 additionally adjusted for systemic comorbidities (arterial hypertension, myocardial infarction, stroke, diabetes mellitus, chronic obstructive pulmonary disease, cancer), ocular diseases (cataract, macular degeneration, corneal diseases, diabetic retinopathy), visual acuity of the worse eye, IOP, antiglaucoma eye medications (Sympathomimetics, Parasympathomimetics, Carbonic anhydrase inhibitors, Beta-blockers, Prostaglandins) and general health status

Challenges

1. Considering that the patient underwent glaucoma surgery using the classical method at the end of 2022 and both eyes were operated on, and after the beginning of 2023, he has not used any eye medication (I mean timolol), so why is it still nearly two years and the patient's psychological condition has not changed and he is still undergoing regular psychological treatments?

2. How should we evaluate the patient's own role in the continuation of his or her disease? Shouldn't we review the theory of Professor William Glasser, a 21st century psychologist, who believes that patients who experience psychological problems at any stage of life go through a choice in this and similar cases?

William Glasser says:

These patients choose to remain in the psychological state. Because they pay less and transfer all the problems and pathogenic factors to outside themselves. They deny their own role. In fact, they pretend that they are

innocent and that outside themselves have created these problems for them. In our case, he focuses on timolol eye drops.

3. The background of these patients cannot be completely rejected or accepted. While the patient's psychological condition is almost stabilized, the question is:

- Can we guide the patient to accept William Glasser's theory or not?

- Will the patient's condition improve or worsen if this is done?

No one can answer these questions and it is very difficult for me to get into this issue. Because I am worried that I will make his condition worse and worse. For this reason, it is a big challenge in itself.

4. Perhaps we can accept in this case that the cause of this patient's psychological symptoms was not primarily due to the use of the drug timolol, but as an independent factor, that is, without the glaucoma patient and the use of timolol drops, which caused the secondary appearance of these psychological symptoms.

That is, patients with glaucoma may be affected by the real threats they face in relation to this disease and may eventually be drawn towards depression, which in our case may be interpretable given that he has not been using this medication for more than two years.

Conclusion

1. Considering that he underwent glaucoma surgery at the end of 2022 and both eyes were operated on and after the beginning of 2023 he has not used any medication for his eyes (meaning timolol), then why is it still nearly two years and the patient's psychological condition has not changed and he is still undergoing regular psychological treatments?

2. How should we evaluate the patient's own role in the continuation of his disease? Shouldn't we review the theory of Professor William Glasser, who believes that patients who experience psychological problems at any time go through a choice discussion, in this case and similar cases?

William Glasser says that these patients choose to remain in the psychological state because they pay less themselves and transfer all the problems and pathogenic factors to outside themselves and deny their own role and in fact pretend that they are innocent and that outside themselves has created these problems for them. In our case, the issue is completely focused on the drug timolol.

3. The background of these patients cannot be completely rejected or accepted, while the patient's condition is almost psychologically stabilized. The question is whether we can lead the patient to accept William Glasser's theory or not? If we do this, will the patient's condition get better or worse than it is now? No one can answer this question and it is very difficult for me to get into this issue because I am worried that I will make his condition worse and worse, which is why it is a big challenge in itself.

4. We may accept that in this case, the cause of this patient's psychological symptoms were not primarily due to the use of the drug timolol, but rather as an independent factor, namely the glaucoma disease, which caused the secondary occurrence of these psychological symptoms and had nothing to do with the drug. This means that patients with glaucoma may be affected by the real threats that this patient finds and eventually be drawn towards depression, which in our case, considering that he has not used this drug for more than a year and a half, may be explainable why the psychological symptoms still remain.

5. Finally, will we one day be able to easily apply Professor Glaser's theory to psychological patients and help them solve their complex problems, regardless of drug or psychological treatments? This question remains unanswered.

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