Neuropsychiatric Adverse Events from Topical Ophthalmic Timolol

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Timolol is a beta-adrenergic receptor blocker that was introduced in the late 1970s in both topical and oral formulations. Chemically, it is a propanolamine compound, and is now one of the most common topical treatments for increased intraocular pressure and glaucoma. Its introduction was initially a major innovation, especially for glaucoma treatment. Indeed, the commonly used glaucoma treatments (topical and oral) preceding timolol (eg, pilocarpine, epinephrine, and acetazolamide) were commonly complicated with problematic side effects.

Timolol is a non-selective beta-blocker. Its receptor blockade is reversible, but it is nonetheless long-acting. Both topically and systemically, its activity occurs typically in approximately 20 to 30 minutes. In the late 1970s, it had been already determined that timolol was superior to other beta-blockers for topical glaucoma treatment. After ocular administration, up to 80% of the ocular dose can be systemically absorbed through the nasal mucosa. Nevertheless, some 12% to 88% of an ocular dose may be lost to eyelid overflow prior to any such absorption. Over 65% of peripheral beta-receptors will be saturated through such systemic absorption on an incremental basis. Cumulative blood levels may reach the range of 0.2 µg/L to 9 µg/L after the use of either 0.25% or 0.5% ophthalmic solutions, but typically blood levels are less than 2 µg/L. With a half-life of approximately 5 hours, residual activity persists well past the usual 12-hour dosing interval and possibly up to 24 hours. Peak local pharmacological activity is found after approximately 2 hours. When given orally, timolol is subject to metabolism in a first-pass effect through the liver (up to 40%), but such metabolic processing is negligible after ocular administration and nasal absorption. Volunteers given an intravenous dose of 0.25 mg have had blood levels comparable to those achieved after topical use. In contrast, an oral dose of 20 mg (oral dosing usually 10 mg to 20 mg) will yield plasma levels of approximately 50 µg/L to 100 µg/L, although residual plasma levels decreased to approximately 1 µg/L to 7 µg/L 12 hours later. Blood levels
after ocular administration can remain high among the elderly and among those patients who have metabolic defects for beta-blocker metabolism. Children often have the higher blood levels. Ocular timolol can conceivably complicate the existing beta-blockade of other orally administered beta-blockers. Both topical and systemically absorbed timolol functionally reduce aqueous humor production and, hence, ameliorate glaucoma through a reduced availability of intraocular fluid. Topical timolol applied to one eye is capable of some pressure reduction in the contralateral eye.

Of those given timolol in any topical format, 6% to 13% will terminate use for various reasons, albeit mainly ophthalmological. The magnitude of systemic absorption gives credence to the possibility of early systemic events such as the lowering of blood pressure and reduction of heart rate. Beta-blockade of a non-selective nature can induce bronchospasm in those so predisposed to reversible airways disease. Soon after topical timolol was introduced for routine use, central nervous system effects were being tallied.

Neuropsychiatric Events
Publications of the association of central nervous system side effects with oral beta-blockers preceded the introduction of timolol by nearly a decade or so. Some of these adverse reactions included depression and psychosis. Citations were also made of such events among human volunteers who were otherwise previously well. Investigations of the latter led to the proposal that more lipophilic beta-blockers, perhaps with enhanced capacity of entering the central nervous system, could provide a greater risk for neurological events. The latter concept was disputed by a report in which lipophilic and non-lipophilic beta-blockers induced psychosis in one patient. A better understanding of these concepts regarding lipophilic profile and toxicity is required. Despite the scientific findings, there remains some skepticism about a causal relationship.

When oral timolol was used for hypertensive and cardiac patients, episodes of neuropsychiatric events were also recognized. A relationship of increased adverse events with higher blood levels of the drug was suggested. As reactions to topical timolol became apparent, investigators sought to determine if other topical beta-blockers would pose the same risk. For example, topical timolol was compared to topical betaxolol in several studies, and there were more side effects with the former. Not uncommonly, patients terminated their prescriptions with both oral (27.8%) and topical (9%) timolol.

Table 1 highlights case reports of topical timolol-associated central nervous system events. The patients reported in these publications were considerably heterogeneous. Some had a past history of psychiatric problems. Others were complicated by the use of multiple topical pharmacological agents. A few patients clearly had some cardiac events that may secondarily have caused neurological outfall, as some have suggested. Overall, the side effects disappeared after a few hours to a month, which is consistent with the otherwise general experience of beta-blockers. Children of young age are susceptible, although reports are few. Larger studies of topical timolol for infantile glaucoma are lacking. Few reports have validated the causal relationship by challenge and rechallenge observations. Although the nature of these reports would no doubt raise some limitations about ascribing definitive causation, the timeliness of clinical improvement after drug cessation in most circumstances supports a cause and effect relationship.

The nature of adverse events is detailed in Table 2. As a non-ocular system category from a National Registry for Drug-Induced Ocular Side Effects, adverse effects of the central nervous system were most commonly reported. Some patients were unaware of the complications until the medication was stopped. No association has been found with the use of topical beta-blockers and excess mortality, however.

Larger studies that may be relevant to the understanding of neuropsychiatric complaints or findings are detailed in Table 3. Two studies did not conclude there was an association of topical timolol and central nervous system events. Each of the latter acknowledged the limitations of small patient numbers in the study groups. Several studies are based solely on passive reporting or simple observations, and others were structured as retrospective cohorts. Most, if not all, studies could easily be criticized for one or more limitations. Dosing of topical timolol was not consistently detailed in those reports. Few studies utilized a challenge-rechallenge format. Overall, the level or grade of evidence is not consistent with purposeful, well-designed, randomized studies that could have been inclusive of sufficient patient numbers. Nevertheless, although lacking in many regards of study design and observation, the combination of anecdotes and larger studies could lead one to believe that topical timolol is associated with adverse neuropsychiatric events and that due respect should be afforded to this possibility. A further accumulation of supportive data should be pursued.

Of note, one study of 15 randomized trials of various oral beta-blockers in the realm of cardiology treatments did not find an association of use with the onset of depression, fatigue, or sexual dysfunction. The latter report, however, preselected for studies where such side effects were reported. Another study of the existing data on topical beta-blockers, and especially timolol, in 2002 also refuted the association with various side effects, but only depression was assessed among illnesses of the neuropsychiatric spectrum. A major dilemma with the latter approaches, however, was that no systematic prospective studies were then available. Therefore, the clinician is confronted by the refutation of causation based on a lack of data versus the summation of adverse events from general reporting and variable group studies. There is evidently more room for further analyses and hypothesis testing.
| 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, Syncope, visual hallucinations | 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 Amaurosis fugax, transient ischemic attacks | Timolol     | After cessation | Frequent hypoglycemic episodes | No                       | 1983 | 33        |
| 78  | M      | Depression, 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 retri of medication to confirm | No                       | 2017 | 40        |
Table 2. Reported adverse reactions that span the neuropsychiatric spectrum

| Anorexia               | Impotence and other sexual dysfunctions |
|------------------------|-----------------------------------------|
| Anxiety                | Insomnia                                |
| Apnea in neonates      | Libido reduction                         |
| Confusion              | Lightheadedness                          |
| Depression             | Loss of concentration                    |
| Diplopia               | Malaise                                  |
| Disorientation         | Memory loss                              |
| Dissociative behavior  | Myalgia                                  |
| Dizziness              | Myasthenia                               |
| Drowsiness             | Nightmares                               |
| Dysarthria             | Paresthesia                              |
| Dysgeusia              | Peripheral neuropathy                    |
| Euphoria               | Sensory disorder                         |
| Fatigue                | Somnolence                               |
| Hallucinations         | Tinnitus                                 |
| Headache               | Weakness                                 |
| Hypotonia              |                                         |

Remnant Concerns
Could responses to topical timolol be patient specific? Genetic polymorphisms have been linked to beta-blocker efficacy.56 Can modifications of drug use be applicable? The closure of the nasolacrimal duct after topical administration has been suggested to enhance local penetration.12,57 Although the latter might be an appealing tactic to reduce systemic absorption, it is not clear that the neuropsychiatric complications are a function of systemic absorption, penetration of the central nervous system directly through the eye, or any other modality.

It is not uncommon for patients with increased intra-ocular pressure to be elderly. In this patient population, concomitant co-morbidities and frailty generally may confuse the understanding of whether topical timolol is capable of having caused morbidity. When interviewing patients about their drug histories, it is not uncommon for the ophthalmic group to be forgotten in the discussion altogether, and use of topical agents may be overshadowed by other polypharmacy. It is also realistic that physicians will fail to associate a systemic adverse event with a topical ocular solution.

Alterations of topical timolol dosing have not been fully explored. Concerns in this regard parallel the toxicity potential with topical timolol use in pediatric dermatology.58 Newer formulations of timolol will undoubtedly exploit sustained-release administration or mixed drug formulations. It is unclear at this time how such approaches will affect the frequency of neuropsychiatric events. Timolol is now an old drug, relatively speaking, and yet it is among the most commonly, if not the most commonly, used topical agent in this context. It may prove difficult to stimulate further both molecular and clinical research in its use topically given its lack of novelty and attracted funding.

It would be best to give patients the benefit of doubt when central nervous system effects are being considered. Cautious use of topical timolol in at-risk patients is relevant, and careful observation for neuropsychiatric effects should be maintained. Cessation and sufficient observation or challenge-rechallenge strategies are of potential value in confirming a cause and effect relationship. The increasing spectrum and availability of other topical antiglaucoma agents makes the option of cessation and conversion to another pharmacological agent more available, but the issue of adverse events will continue into the foreseeable future given the continuing high frequency of topical timolol use in glaucoma.

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| Study Design          | Findings                                                                 | Measurement             | Limitations          | Timolol Concentration | Challenge-Rechallenge | Level of evidence | Grade of evidence | Year | Ref |
|----------------------|--------------------------------------------------------------------------|-------------------------|----------------------|-----------------------|-----------------------|-------------------|-------------------|------|-----|
| Case series          | 17/165 had CNS side effects, 6/17 discontinued medication                | Active reporting on follow-up | Not confirmatory      | 0.25%, 0.5%           | No                    | V                 | Low               | 1979 | 28  |
| Case series          | 79/547 side effect entries were CNS                                     | Passive registry reporting | Based on reporting only | Not stated            | No                    | V                 | Low               | 1980 | 44  |
| Case series          | 18/489 consecutively treated patients had follow-up CNS side effects    | Active patient          | Not confirmatory      | 0.5%                  | No                    | V                 | Low               | 1980 | 15  |
| Case series          | Wide range of CNS complaints                                            | Passive registry reporting | Based on reporting only | Not stated            | No                    | V                 | Low               | 1983 | 4   |
| Case series          | Wide range of CNS complaints                                            | Passive registry reporting | Based on reporting only | Not stated            | No                    | V                 | Low               | 1987 | 42  |
| Crossover            | 16/18 CNS events improved with change to betaxolol                      | Patients with timolol side effects entered | Small numbers         | 0.5%                  | No                    | IV                | Low               | 1988 | 26  |
| Double-blind         | 5/8 CNS events improved with change to betaxolol                        | Patients with timolol side effects entered | Small numbers         | 0.5%                  | No                    | II                | Moderate          | 1988 | 26  |
| Case series          | 7/40 headache, 6/40 dizziness, 2/40 depression, 2/40 nightmares, 2/40 memory loss | Observational          | Small numbers, no statistics | Not stated            | Few                   | IV                | Low               | 1989 | 24  |
| Double-blind, pilot study | More side effects with timolol than betaxolol                       | Several test batteries  | No statistics         | Not stated            | No                    | II                | Low               | 1989 | 27  |
| Double-blind, cross  | Higher depression scores in timolol group versus betaxolol             | Beck and Zung-Conde inventories | No controls           | 0.5%                  | Few                   | II                | Moderate          | 1992 | 25  |
| Random, double-blind, mult-center | 0/50 with timolol treatment had CNS events; depression and somatization scores not changed before and after treatment | Psychological checklist (SLL-90-R) | Small numbers         | 0.5%                  | No                    | II                | Moderate          | 1999 | 47  |
| Cohort studies       | No association of beta-blocker and depression                           | Self-survey questionnaires | Small numbers         | Not stated            | No                    | III               | Low               | 2002 | 48  |
| Case-control         | 9.2% of those on timolol had positive scores for major depression; approx. five times more depression than control group | Self-given questionnaires | No control matching   | Variable              | No                    | III               | Moderate          | 2011 | 49  |
| Cohort studies       | Increased risk of starting antidepressants after topical timolol use    | Adjusted sequence ratio | Retrospective         | Not stated            | No                    | III               | Moderate          | 2012 | 50  |
| Random, double-blind, mult-center | 3.8% of those on timolol had nervous system disorders                   | Patient reporting       | Prospective but no controls | 0.5%                  | No                    | III               | Moderate          | 2018 | 51  |

[Level of evidence is considered in five categories: Level I – large randomized trials with clear-cut results, Level II – small randomized trials with uncertain results, Level III – nonrandomized, contemporaneous controls, Level IV – nonrandomized, historical controls, Level V – no control, case-series only] [Grade of evidence is defined in four categories: High – further research is unlikely to change our confidence in the estimate of effect, Moderate – further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate, Low – further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate, Very Low – any estimate of effect is very uncertain]
| Study                          | Timolol | Challenge Level | Level of Evidence | Concentration | Evidence | Year | Ref |
|-------------------------------|---------|----------------|-------------------|---------------|----------|------|-----|
| Active reporting on passive registry only |         |                | Low               | 0.25%,0.5% | No V    | 1979 | 28  |
| Active patient reporting only based on reporting |         |                | Low               | Not stated   | No V    | 1980 | 15  |
| Beck and Zung-Conde inventories no controls |         |                | Moderate           | 0.5%         | Few II  | 1992 | 25  |
| Psychological checklist Small numbers |         |                | Moderate           | 0.5%         | No II   | 1999 | 47  |
| Random, double-blind, multi-center No association of beta-blocker and studies |         |                | Low               | Not stated   | No III  | 2002 | 48  |
| Random, double-blind, retrospective No association of beta-blockers and acute psychosis |         |                | Moderate           | Small numbers | Not stated | 2011 | 49  |
| Random, double-blind, multi-center No association of beta-blockers and acute psychosis |         |                | Low               | Small numbers | Not stated | 2012 | 50  |

Level of evidence is considered in five categories: Level I – large randomized trials with clear-cut results, Level II – small randomized trials with uncertain results, Level III – nonrandomized, research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate, Very Low – any estimate of effect is very uncertain.
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