

Lithium Decreases Retinal Sensitivity, but This Is Not Cumulative with Years of Treatment

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Introduction

Lithium salts are successfully used in the treatment of manic-depressive and recurrent depressive illness. The mechanism of action is still unknown, though clearly linked with effects on neurotransmission in the central nervous system (CNS) (particularly at the membrane and second-messenger level), and as modulator of circadian rhythms (for literature review, see Lam et al 1997, this issue). In addition, functions of the retina, also a CNS tissue, are modulated by lithium. In animal experiments, lithium affects the retina on a structural (Remé et al 1988), biochemical (Pfeilschifter et al 1988; Jung and Remé 1994), and electrophysiological (Bush and Remé 1992) level, as well as modifying retinal input to the circadian timekeeping system (Terman et al 1991). These findings led to worries that patients on lithium may be vulnerable to retinal damage should they undergo light therapy. In an initial case study, a lithium-treated patient with recurrent winter depression required 3 weeks of light exposure instead of the usual 3-4 days to initiate therapeutic response (Wirz-Justice and Haug 1991). Her retinal light sensitivity as measured by automated perimetry was decreased. When, after some winters, she stopped taking lithium, the light response was rapid.

Methods

Ophthalmology

To clarify the visual status of long-term lithium-treated patients, we thus initiated a study in two University Eye Clinics, using identical methods (G1 program of the Octopus 500EZ[®] automated perimeter and dark adaptation with the Goldmann-Weekers instrument, using standard procedures) as well as additional techniques [color recognition thresholds and contrast sensitivity functions in Zürich (Huber 1989), standard electroretinogram (ERG) and electro-oculogram (EOG) in Basel (performed on a Nicolet C15 Ganzfeld system following International Society for the Clinical Electrophysiology of Vision standards)]. Patients had no complaints of visual problems or history of eye disease. The initial testing revealed a range of visual acuity of 0.7-1.0, as well as 12 patients with age-related cataracts, 1 patient with diabetic retinopathy, and 1 patient with glaucoma (excluded from some of the tests). For various reasons, technical or individual, not all subjects completed all tests.

Diagnoses

Patients were recruited from lists of both cities' lithium clinics and were given a complete, free ophthalmological testing as incentive for participation. Data were similar from both centers, and thus combined (preliminary reports in Prünfte et al 1990; Remé et al 1991).

A total of 71 patients (27 men, 44 women, mean age 54.8 years, range 23-80), whose diagnoses had been previously

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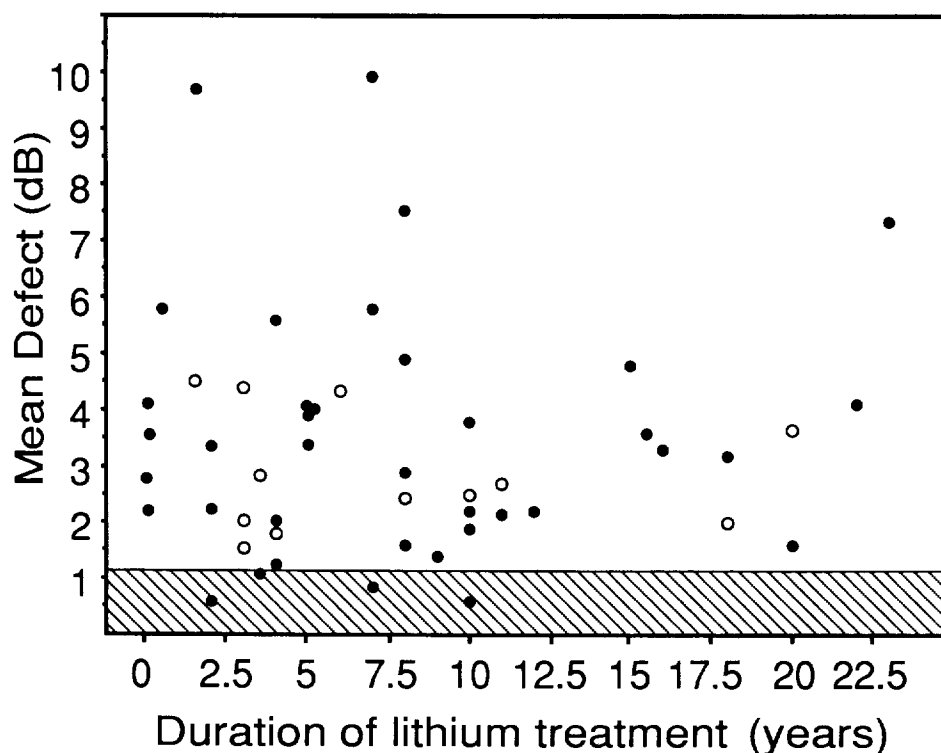


Figure 1. Individual values for the mean defect in decibels, dB (as measured by automated perimetry, G1 program) according to years of lithium treatment. Open circles represent patients on monotherapy with lithium alone; closed circles represent lithium plus other psychopharmacologic treatment. The stippled area represents the upper 1 SD limit of a healthy population studied under the same conditions ($n = 552$, -0.3 ± 1.4 dB, range -2 – $+2$ dB), showing how few of the lithium-treated patients fall within this range.

established by a psychiatrist (ICD-9 296.0–296.3 and 295.7), were in ambulatory medical care, euthymic, and had been taking lithium for 1 week–23 years. Only 12 could be found on monotherapy with lithium; the others were additionally treated with tricyclic antidepressants and benzodiazepines, and a few with neuroleptics. In all ophthalmologic measures reported here, the 12 lithium-treated patients were no different from the lithium plus other medications group, and thus the data were combined.

Results

For analysis of the automated perimetry the collective was reduced to 50 (exclusion criteria: hypertonia, diabetic retinopathy, cataract, refractive errors with a spherical correction > 5 diopters or a cylindrical correction > 2 diopters, low cooperation). The only consistent effect was that patients had an increase in visual field mean defect, i.e., decreased sensitivity to light compared with an age-matched normal control group. In all patients a diffuse damage of the visual field without total scotomas was observed. This was neither correlated with age ($r = .21$, ns) nor, importantly for the clinician, was this dependent on treatment duration ($r = .02$, ns) (Figure 1).

Complete scotopic dark adaptation thresholds were available

for 67 patients. These were compared with age-matched controls in the clinics' database. Age itself increased the dark adaptation threshold, and there was an interaction between the controls and patients with respect to the time course of adaptation [$F(6, 576) = 6.1$, $p < .0001$]. If the values for cone adaptation (taken at 5') were separated from the rod adaptation thresholds (at 30'), lithium-treated patients showed lower values than controls for the cone adaptation threshold [controls ($n = 33$), 6.29 ± 0.28 (SD) log units; patients ($n = 67$), 5.85 ± 0.61 log units; $F(1, 94) = 2.0$, $p < .0001$], but higher values for the rod adaptation threshold [controls, 2.27 ± 0.30 log units; patients, 2.59 ± 0.46 log units; $F(1, 94) = 7.28$, $p < .008$]. Again, there was no significant correlation between changes in the dark adaptation threshold and the duration of lithium treatment.

Color recognition thresholds were raised in 23 of 30 patients tested. Interestingly, there were no abnormalities in the contrast sensitivity function in any of the patients.

There were no marked abnormalities in the EOG, except for increased frequency of fixation saccades. The Arden Index in the patient group with combined treatment ($n = 72$ eyes) was 1.75 ± 0.31 ; lithium alone ($n = 8$ eyes) = 1.7 ± 0.14 ; control subjects ($n = 48$ eyes) = 1.89 ± 0.25 (Figure 2). There was no correlation with length of lithium treatment ($r = .09$, ns).

The scotopic ERGs were also normal ($n = 38$ – 40). The latency of the b-wave was 86.3 ± 7.8 msec (right eye) and

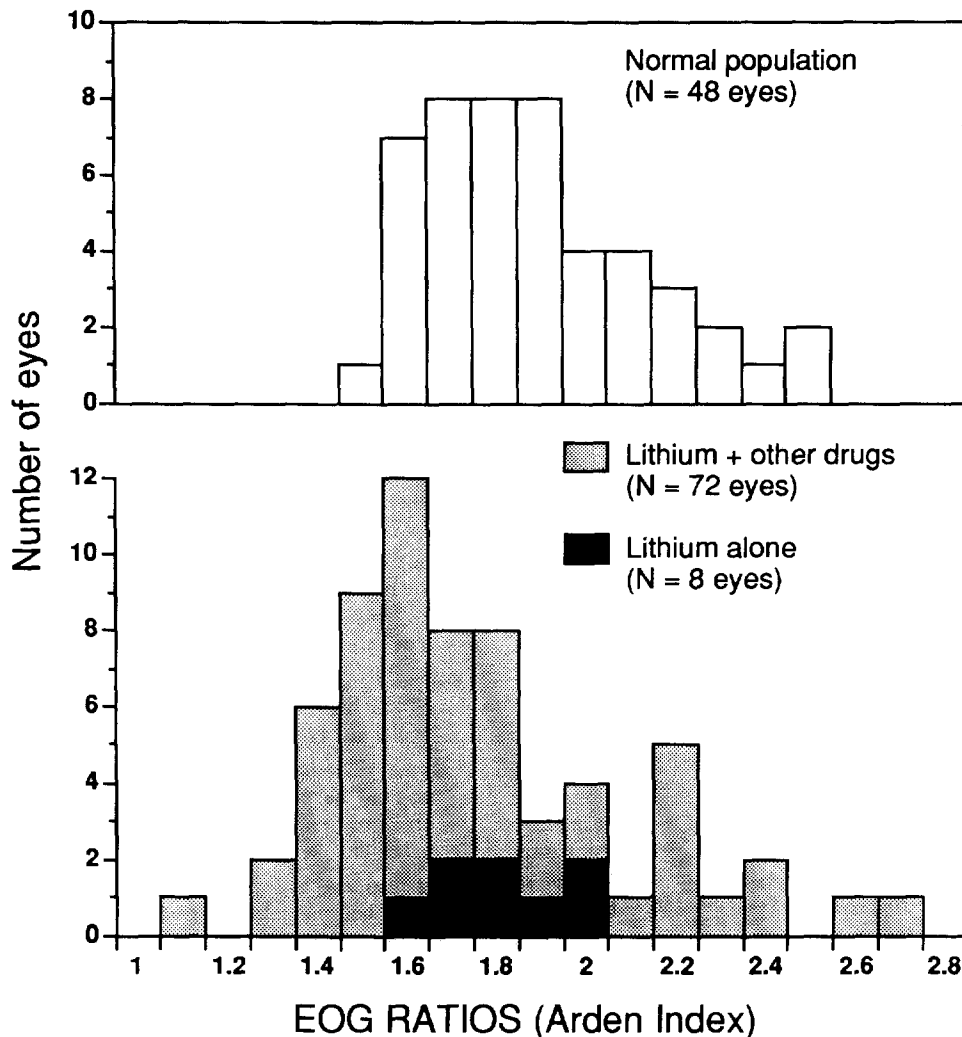


Figure 2. Comparison of the Arden Index in a normal population (upper panel: normal values are an EOG ratio > 1.5) with that of the patient groups (lower panel).

85.3 ± 6.3 msec (left eye), compared with our prior established range of values for healthy subjects of 76.1–94.8 msec. The amplitude of the b-wave was 154.6 ± 67.5 μV (right eye) and 161.3 ± 50.9 μV (left eye), which compares with our previous control values of 142–402 μV. As an example of the photopic measures, the 30 Hz-flicker response was also normal: patients (n = 25) showed a latency of 91.73 ± 2.27 msec (right eye), 91.86 ± 2.62 (left eye), and an amplitude of 112.70 ± 29.81 μV (right eye), 106.3 ± 30.36 μV (left eye). Although single eyes showed longer latencies or lower amplitude, these were not constant over all conditions and not correlated with lithium treatment duration.

Discussion

Concerning medical practice, lithium-treated patients may be at higher risk of acquiring acute photoreceptor lesions while ex-

posed to bright light for repeated or for prolonged periods. This may occur naturally (e.g., outdoor occupations) or with artificial light therapy for winter depression; however, in the 25 years of lithium use as a prophylactic agent, remarkably few patients have complained of visual impairments. The subtle but significant findings here indicate reduction of light input (e.g., lithium as “pharmacologic sunglasses”), and perhaps less efficient response for complex visual tasks involving color recognition.

Thus, lithium enhances acute, light-induced retinal alterations in animals but reduces visual sensitivity in humans. Whether the gradual cell damage observed in morphological studies (Remé et al 1988) underlies the psychophysical changes remains to be elucidated. A combination of lithium effects on retinal neurotransmission and cell loss is also possible.

These findings do not assess the long-term cumulative risk of combining lithium treatment with light therapy, assessed over

decades. In these cases, ophthalmologic safety precautions should be followed (see Gallin et al 1994; Remé et al 1996).

In conclusion, this complete and extensive ophthalmological testing of a large group of lithium-treated outpatients revealed few and subtle modifications of visual function. That the effect was not augmented with duration of treatment, is a comforting index of lack of cumulative and degenerating effects on the visual system.

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