Effects of Chronic Aripiprazole and Trazodone Treatment on Lens Opacity and Oxidative Stress in Female Rats

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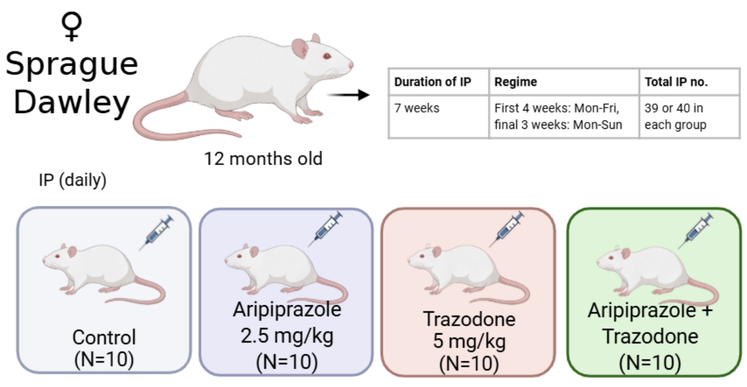
BACKGROUND

Oxidative stress is a key mechanism contributing to lens protein and lipid damage and subsequent loss of lens transparency. Although psychotropic medications are widely used, their potential effects on lens redox homeostasis remain insufficiently investigated. This study aimed to determine whether chronic administration of aripiprazole and trazodone, alone or in combination, affected lens opacity and oxidative stress in middle-aged female rats (Figure 1).



Duration of IP	Regime	Total IP no.
7 weeks	First 4 weeks: Mon-Fri, final 3 weeks: Mon-Sun	39 or 40 in each group

Figure 1. Study design

METHODS

Forty-one female Sprague-Dawley rats (11–12 months old) were randomly assigned to four groups: control (5% DMSO), aripiprazole (ARI, 2.5 mg/kg), trazodone (TRZ, 5 mg/kg), and combined treatment (ARI+TRZ). Drugs were administered intraperitoneally for 7 weeks. After euthanasia, right lenses were dissected, photographed, weighed, snap-frozen, and stored at −80 °C. Lens opacity was quantified as mean grayscale intensity (0–255) using ImageJ. Left lenses were homogenized for oxidative stress analyses, including thiobarbituric acid reactive substances (TBARS), reduced glutathione (GSH), and glutathione peroxidase (GPx) activity, measured spectrophotometrically at 532, 412, and 340 nm, respectively. Oxidative stress parameters were analysed by one-way ANOVA with Tukey's multiple-comparisons test, while lens opacity and weight were analysed using Welch's one-way ANOVA with Games-Howell *post hoc* testing. Statistical significance was set at $p < 0.05$.

RESULTS

All treatment groups exhibited significantly greater lens opacity than controls ($p < 0.05$) (Figures 2 and 3), with the combination treatment producing greater opacity than aripiprazole alone. Lens mass was higher in the trazodone and combination groups than in controls (Figure 4). Lens opacity correlated strongly with lens mass ($r = 0.812$, $p < 0.0001$), indicating an association between opacity and lens mass (Figure 5). To compare oxidative stress markers, TBARS, GSH, and GPx values were normalized to the control mean and expressed as a percentage of control (100%). All treated groups showed significantly elevated TBARS levels ($p < 0.05$), with the highest values in the aripiprazole plus trazodone group. GSH levels decreased progressively across treatment groups, while GPx activity was slightly increased by aripiprazole but reduced by trazodone and combination treatment. Overall, these results indicate increased oxidative stress and impaired antioxidant defense, particularly following combined treatment (Figure 6).

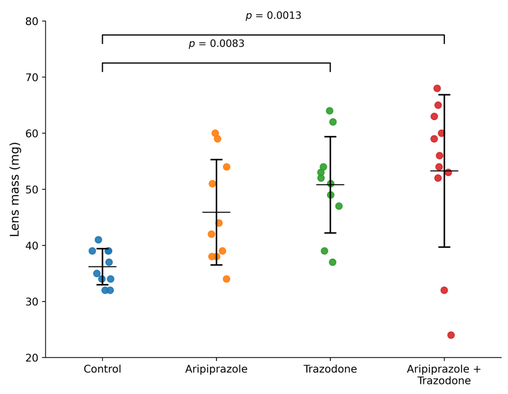


Figure 4. Effect of aripiprazole and trazodone treatment on lens mass. Individual lens mass measurements are shown for each animal. Horizontal lines indicate group means, and error bars represent standard deviations (SD)

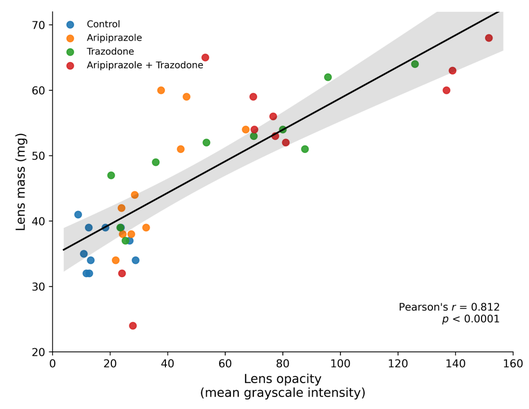


Figure 5. Association between lens opacity and lens mass. Scatter plot showing the relationship between lens opacity, expressed as mean grayscale intensity, and lens mass across all experimental animals. The solid line represents the overall linear regression fit, and the shaded area indicates the 95% con-fidence interval.

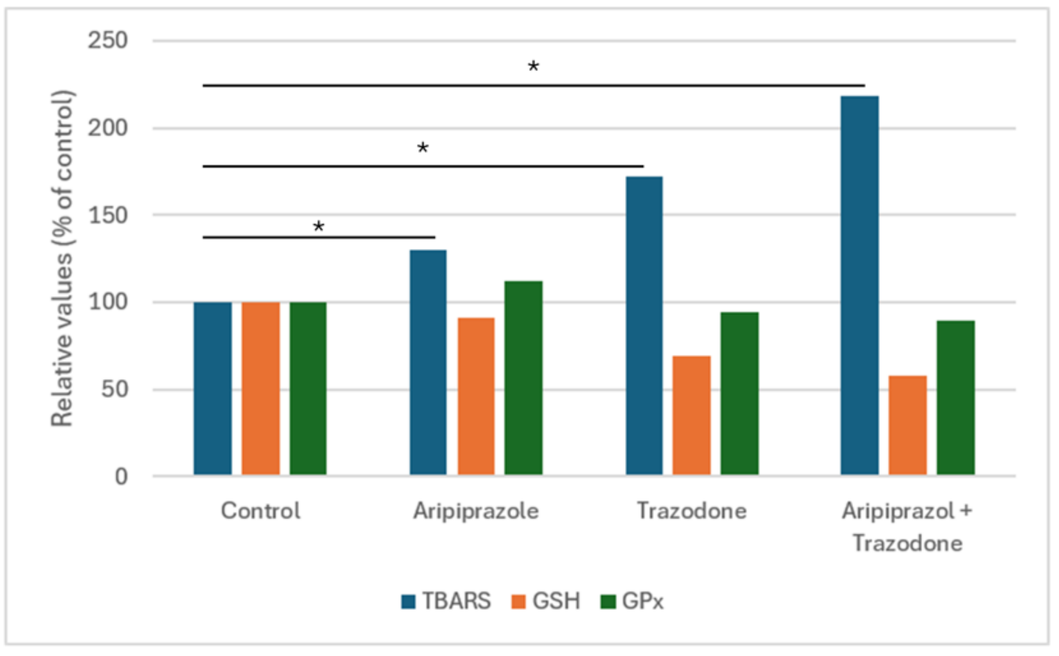


Figure 6. Effects of chronic aripiprazole and trazodone treatment on lens oxidative stress parameters.

DISCUSSION

Chronic aripiprazole and trazodone treatment increased lens opacity and disrupted lens redox homeostasis: elevated TBARS and reduced antioxidant defense. The strongest effects were observed following combined treatment, suggesting additive or synergistic oxidative damage. These findings are consistent with our previous studies demonstrating that aripiprazole and trazodone inhibit DHCR7 and increase 7-dehydrocholesterol (7-DHC) levels in the brain, peripheral tissues, and serum. Because 7-DHC is one of the most oxidation-prone biological lipids, its accumulation may increase susceptibility to oxidative damage and contribute to the generation of reactive oxysterols. Although sterol composition was not examined in the present study, the observed increase in lipid peroxidation together with depletion of glutathione supports the possibility that altered sterol homeostasis contributes to lens oxidative stress. The strong positive correlation between lens opacity and lens mass further suggests that oxidative imbalance is associated with structural lens changes. These findings suggest that oxidative stress and altered sterol metabolism contribute to drug-induced lens opacification.

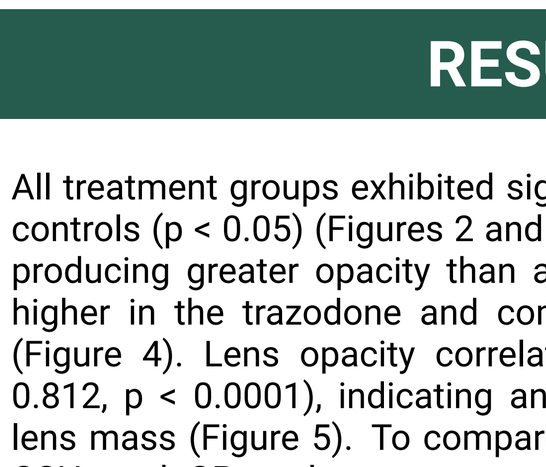


Figure 2. Photographs of isolated lenses from each experimental group. Representative lenses from (A) control, (B) aripiprazole, (C) trazodone, and (D) aripiprazole + trazodone groups photographed against a black background.

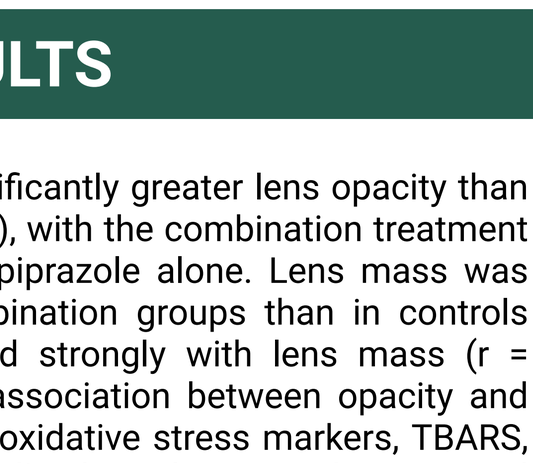


Figure 3. Effect of aripiprazole and trazodone treatment on lens opacity. Individual lens opacity measurements are shown. Horizontal lines indicate group means, and error bars represent standard deviations (SD).

ACKNOWLEDGEMENTS

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