THE EFFECT OF TEMPERATURE CHANGE ON THE PH OF COMMON OPHTHALMIC SOLUTIONS

by

Elena M. Rose

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Elena M. Rose

Has been approved

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APPROVED:

[redacted]

Faculty Advisor

ACCEPTED:

[redacted]

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ABSTRACT

Background: This research study serves to explore potential trends in temperature and pH as it relates to pharmaceutical standards of ocular medications. The goal is to create useful suggestions for patients in order to encourage good compliance with ophthalmic drops by helping alleviate any discomfort through a simple change in temperature. ***Methods:*** The ophthalmic solutions used in this study include: Durezol®, Moxeza®, Simbrinza®, Tobradex®, and Travatan Z®. Using an electronic pH meter, the pH of various ophthalmic solutions was measured at five different temperatures (very cold, cold, room, warm, very warm) compared to the manufacturer's suggested temperatures. The range of temperatures is based on realistic temperature scenarios in which patients may store their drops. ***Results:*** The pH of each drop varied slightly with temperature. However, a trend of pH change was not found among these five drops. The pH of each drop varied without relatable patterns. ***Conclusion:*** From this study, the temperature/pH relationship alone does not provide enough information to easily find trends among the data. At this time, this empirical data is not enough to confidently make standard suggestions to patients regarding what type of temperature change would make the ophthalmic drop more comfortable. However future studies on this topic including subjective responses from patients may be a valuable asset to patient education in ocular disease management.

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INTRODUCTION

Modern medicine has presented today's patients with opportunities to treat diseases more effectively than ever before. In eye care, diseases that were once visually devastating can largely be managed by simple interventions. Diseases like glaucoma, staph infections, and macular edema can now be controlled with something as simple as an eye drop. However, effective management of disease is met with the major obstacle of patient compliance. Due to the sensitivity of the ocular surface, patients often become noncompliant with instilling the therapeutic eye drops because of the subjective discomfort that is associated with it. In response, many eye care practitioners provide suggestions to their patients to help make the drops more comfortable. The most common suggestions revolve around changing the temperature of the drop. Chemically, changing the temperature of a solution may change the pH of the solution. This change in pH could be related to a patient's tolerance to a given eye drop. The research conducted for this study revolved around real life scenarios involving an eye drop's temperature change and its effect on pH. The purpose of this study was to create a useful piece of patient education regarding ways to increase a patient's subjective comfort with a therapeutic eye drop, and thus positively impact compliance with medical interventions in ocular disease.

BACKGROUND

Of the common "five senses", sight is arguably one of the most crucial parts of a human's ability to interact with the world around them. Unfortunately, many known diseases threaten to take a human's ability to see through degenerative processes, infectious courses,

and inflammatory events. Diseases such as glaucoma, corneal ulcers, and uveitis are just a few of the diseases that threaten vision in some form or another throughout their course. Luckily, developments in modern medicine have minimized the incidence of vision loss from these potentially devastating diseases.

The eye care industry revolves around the common goal of effectively managing ocular disease in order to preserve and protect and vision ocular health. Eye care professionals achieve this goal through both optical correction and pharmaceutical intervention. The most common modality of drug administration for managing ocular diseases is the ophthalmic drop. The average individual drop of ophthalmic medication from a typical dropper tip measures 20-50 µL in volume.[1] Medications are dosed according to the type of drug and what ocular pathology is being treated. In office, the doctor generally prescribes the treatment and educates the patient on the dosage regimen that will best control the given ocular pathology. In the ideal case, the patient abides by the recommendations of the eye care professional and the goal of preservation of ocular health is met. However, this is not always the case.

One of the greatest challenges in managing ocular diseases is simply patient compliance.[2] One study, which included an electronic medication monitor showed that up to 15% of the patients omitted 50% of prescribed doses.[3] There are many different reasons for patient non-compliance, including: cost, lack of dexterity, intangible therapeutic effect, and forgetting.[4,5] One of the most common reasons heard by eye care professionals is the "sting" associated with instilling the eye drop.

The patients' feelings of discomfort are understandable. The cornea houses the densest sensory nerve bed in the body, and any assault on the delicate physiology of the cornea will certainly cause a subjective perception of discomfort. Furthermore, the discomfort causes reflex lacrimation which causes much of the drop to be diluted and/or washed away from the ocular surface. Unfortunately, the "sting" is an inherent property in most ophthalmic medication. Anecdotally, some eye care providers recommend refrigerating drops while others have suggested that keeping medications at room temperature or warmer can provide improved subjective comfort.

Chemically, a change in the temperature of a solution will tend to change the pH of the solution. Recall that the pH of a solution is the measure of the free hydronium ions in solution. Higher measurements of hydronium ions yield lower the pH readings, creating a more acidic solution. Ideally for comfort, the pH of an eye drop would mimic that of the natural tears at around 7.4. However, most ophthalmic drugs are salts of weak bases and are most stable for storage at a relatively acidic pH level.[1] As a result, drug manufacturers have had to create a balance between chemical stability and ocular tolerance in order to maximize the impact of their drug on the consumer.

MATERIALS

In this study, five different drops were tested for pH and temperature changes including: Durezol®, Moxeza®, Simbrinza®, Tobradex®, and Travatan Z®. All of the drops used were manufactured by Alcon, however, the purpose of this study was not to collect manufacturer specific data. Rather, the goal in choosing all Alcon products was to minimize as many confounding factors as possible. In addition, the drops were chosen based on the fact that they were very commonly used at this particular clinic site. For this study, a 4mL sample of each drop was used. A total of five pH/temperature measurements were taken per drop in the study, bringing to total data set to 25 different pH/temperature readings. Their specifications from the manufacturer's package inserts can be found in **Table A** below.

To measure the temperature and pH of the drop samples, we used a Milwaukee brand model MW102 pH meter, which includes a built in pH electrode and temperature probe. The electrode and temperature probe were calibrated using the buffers included with the pH meter (pH 7.01, pH 4.01).

METHODS

The different temperature ranges were chosen based on realistic scenarios of eye drop storage once the patient leaves the office with the drop. The different temperature scenarios are detailed below and are empirically related to the manufacturer's temperature suggestions from the package insert of each of the drops. **Table A** below shows information gathered from the package inserts that are relevant to this study.

Table A. Package Insert Information

DROP NAME	MIXTURE	USE	PH LISTED	SUGG'D TEMP
Durezol (difluprednate)	emulsion	anti-imflammatory	5.2 - 5.8	15 - 25°C (59 - 77°F)
Moxeza (moxifloxacin)	solution	antibiotic	7.4	2 - 25°C (36 - 77°F)
Simbrinza (brinzolamide/brimonidine tartrate)	suspension	anti-glaucoma	6.5	2 - 25°C (36 - 77°F)
Tobradex (tobramycin/dexamethasone)	suspension	antibiotic/steroid	5.7	2 - 25°C (36 - 77°F)
Travatan Z (travoprost)	solution	anti-glaucoma	5.7	2 - 25°C (36 - 77°F)

The first measurement on each drop was made at room temperature, which is an expected standard at most clinic offices. This "ROOM" temperature range falls well within the storage range suggested by the manufacturer. The second measurement was made after the drops had been refrigerated to reach a temperature on the low end of the manufacturer's suggested range, but still within it. This "LOW" temperature scenario mimicked how the drop would be stored in a patient's standard refrigerator at their home. The drops were stored for 4 hours in the refrigerator with a temperature of 4.4˚C (40°F). The third measurement was taken after the drops had been cooled beyond the lowest temperature as suggested by the manufacturer. This "VERY LOW" scenario was created to simulate the status of the drop as if they had been left in the patient's car during a cold winter day, where ambient temperatures drop below freezing. The fourth measurement was taken after the drops had been warmed to a temperature on the high end of the manufacturer's suggested range, but still within it. This "WARM" scenario was chosen to simulate the temperature change that might occur as if a patient carried the drop in their pocket, throughout the day, which would warm the drop with their ambient body temperature. The fifth, and final, measurement was taken after the drops had been warmed to a temperature outside the high end of the manufacturer's suggested range. This "VERY WARM" temperature scenario was made to simulate the status of the drop

as if they had been left in the patient's car during a hot summer day. In direct sunlight, a patient's car interior can easily reach from 55°C to 78°C, and any eye drops left in the car for even an hour can reach temperatures outside of the suggested range.[6]

RESULTS

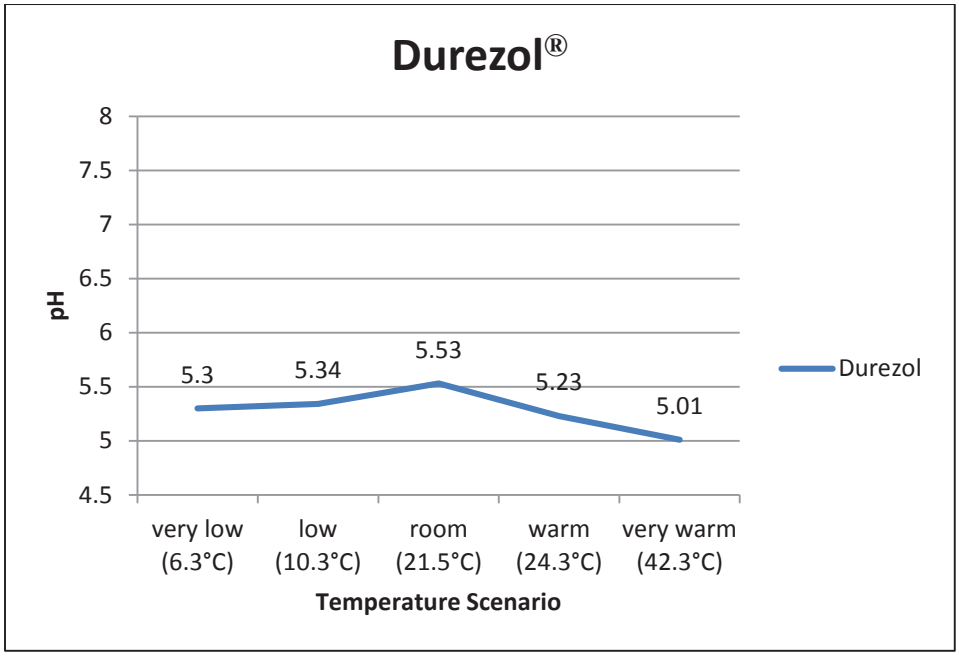
For each temperature scenario, a small range of reasonable temperatures was accepted rounded to the nearest 0.01°C. The temperature readings for each scenario have been gathered in **Table B** and compared to the suggested storage temperature from the package inserts for each drop. Each of the temperatures at which pH data was gathered falls into one of the temperature scenarios as described previously.

Table B. Temperature Readings in Each Temperature Scenario

DROP NAME	SUGG'D TEMP (°C)	VERY LOW (°C)	LOW (°C)	ROOM (°C)	WARM (°C)	VERY WARM (°C)
Durezol	15 - 25	6.3	10.3	21.5	24.3	42.3
Moxeza	2 - 25	0.9	10.2	21.3	24.4	41.5
Simbrinza	2 - 25	1.7	10.5	21.0	24.3	42.3
Tobradex	2 - 25	1.1	10.7	21.2	23.6	41.5
Travatan Z	2 - 25	0.8	11.2	21.3	24.4	41.8

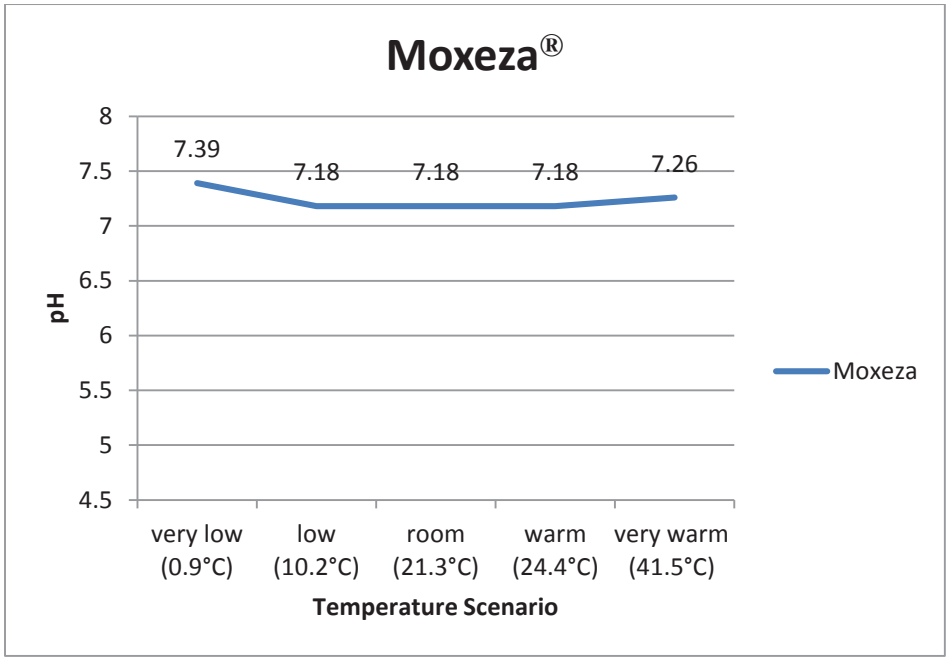
The samples were measured at the various temperature ranges and the following results below show the pH trends gathered for each of the drops individually in **Figure 1 through Figure 5**. On the x-axis of each graph is the temperature scenario and the actual measured temperature. On the y-axis is a consistent pH range from 4.5 to 8.0 to allow for easy comparison of the characteristics of the different drops. In addition, the pH data points are plotted on the graphs for a more specific look at the temperature/pH trend.

Figure 1. DUREZOL®



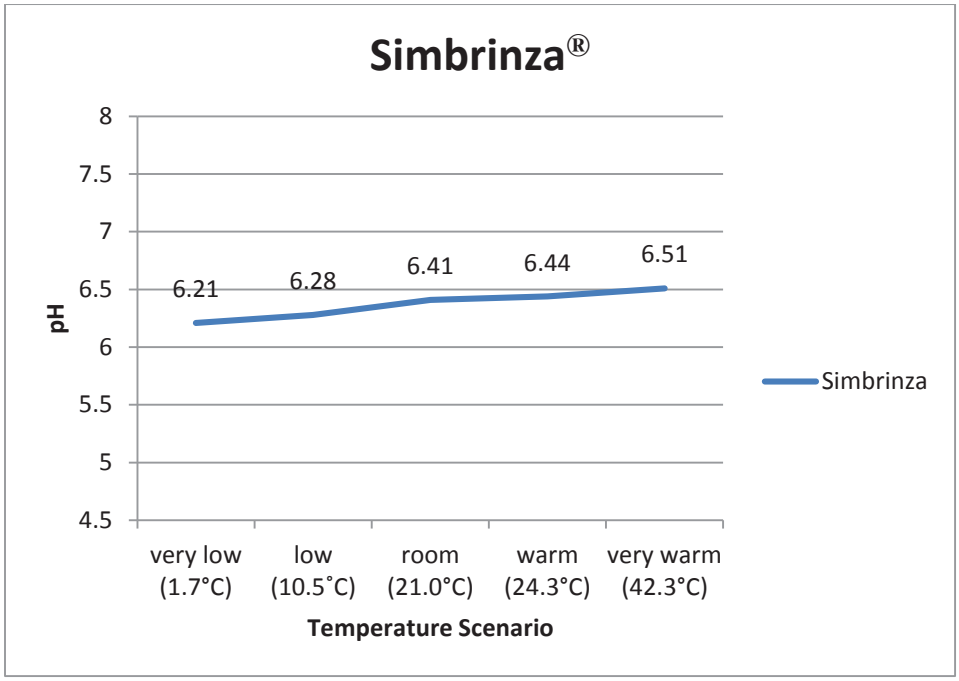
Durezol® did not show any consistent trend in pH change due to varied temperature. The amount of change in pH values from lowest to highest was 0.52. This drop tends is of moderate acidic status compared to the other samples.

Figure 2. MOXEZA®



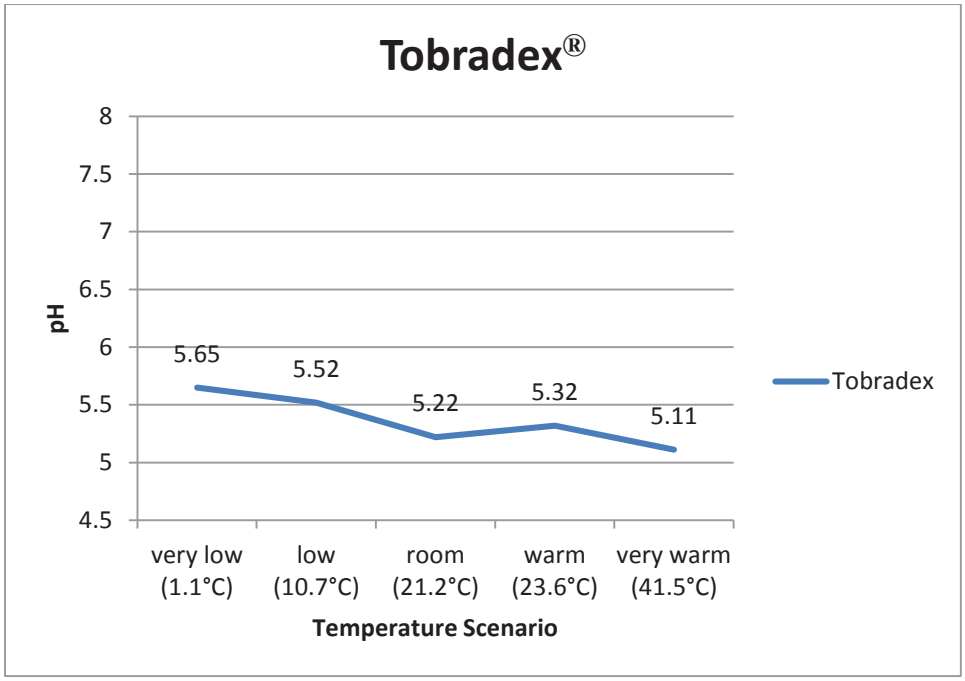
Moxeza® varied the least among all of the drop samples, however no consistent relationship is seen regarding pH change due to varied temperature. The amount of change in pH values from lowest to highest was 0.21. This drop had pH readings closest to that of the physiologic pH of the natural tears of 7.4

Figure 3. SIMBRINZA®



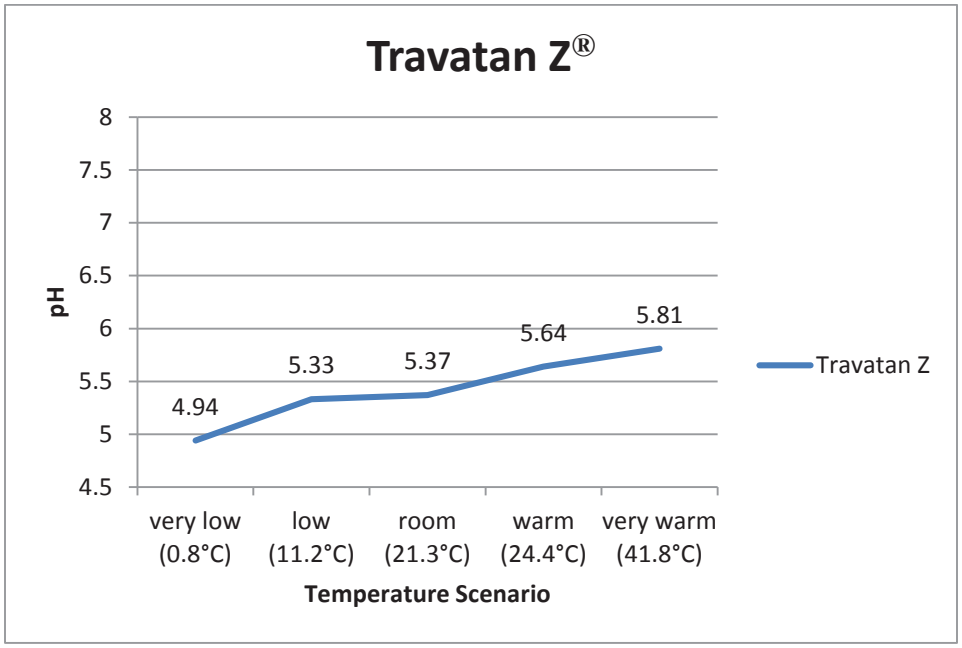
Simbrinza® showed a slight linear trend in pH change due to varied temperature. The amount of change in pH values from lowest temperature to highest was 0.30. This drop became slightly more basic as temperature increased. This drop shows a slight trend towards physiological pH of the tears as temperature increase.

Figure 4. TOBRADEX®



Tobradex® showed a decreasing trend in pH with change in temperature. As one would expect with traditional pH principles, as the temperature increased, the amount of free hydronium ions increased which decreased the pH reading. The amount of change in pH values from lowest to highest was 0.54.

Figure 5. TRAVATAN Z



Travatan Z® reaches the most acidic pH values of all samples, however it showed a substantial linear trend towards becoming more basic with increasing temperature. This drop showed the most variation in pH with temperature change. The amount of change in pH values from lowest to highest was 0.87.

DISCUSSION

This study did not yield clear information about trends that can be predicted and applied to the relationship between pH and temperature of ophthalmic drops. The data showed interesting variations among the five samples and concluded only that temperature does, in fact, affect the pH of the drops even though very slightly. Only Tobradex showed the initially expected trend in pH, becoming more acidic as temperatures increased. In fact, the progressively basic trends found for Simbrinza® and Travatan Z® were contrary to my initial hypotheses about the pH/temperature relationship. As these drops were heated, they became more basic, with Travatan Z® showing the largest effect of temperature of all five samples. Moxeza® did now show a significant amount of change with temperature. This drop began as, and remained, the most basic drop in the study. This stability could be related to the fact that Moxeza® sample was significantly more viscous than the other drops and did not change temperatures easily.

In general, the stability in the pH of the drops is likely due to the buffering ingredient in ophthalmic drops. The buffer is included to keep the drop at the optimum balance during storage while still allowing adequate supply of the active ingredients upon instillation into the eye. The constancy provided by the buffer maintains the life of the relatively volatile active ingredients to a reasonable and useful timeframe.

While the research did not clarify any trends among the data points, it seems as though the information could be used and extrapolated upon for future studies. One of the most important shortcomings of this research was the absence of a subjective component regarding the temperature of the drop. Gathering the opinions of a large patient base regarding the comfort at various temperatures would more easily allow for suggestions to be made to future patients. Each patient's cornea certainly

has a different tolerance to discomfort, however, with a large enough sample size it would be interesting to see if different classes of drops are optimally comfortable at a certain temperature scenario. For example, are prostaglandin analogs more comfortable after being stored in the patient's pocket for a time before instillation? Knowing the pH status of the drop in storage is valuable as subjective research is conducted. The pH of the drop will change as it interacts with the ocular surface and it would be valuable to relate subjective comfort to on-eye pH changes.

When learning about this topic, it became clear that there were not many studies regarding the effect of temperature on pH of ophthalmic drops and the effect on the eye. This topic seems to be a great opportunity to learn more about the chemical and physiological reactions to ophthalmic drops. Some confounding factors in this research should be modified in future studies. First, the sample of 4 mL drops was created by combining smaller volumes of drops from different bottles. This inherently adds variation within the sample itself. In addition, the length of time that a sample was exposed to a temperature scenario and consistency of heating may be useful to explore. This study only allowed the drops to quickly reach the desired temperature before the temperature scenario was changed.

Furthermore, using only one category of drop to further homogenize the sample group would certainly be of value. The samples for this study were based only on common use at this clinical location. Conducting a study on drugs that are closely related to each other could uncover pH trends specific to that family of drops. For example, Travatan Z showed a steady trend towards becoming more basic as the temperature increased and it may be interesting to analyze the pH behavior of other prostaglandin analogs with similar characteristics.

CONCLUSION

Patient compliance is an issue facing not only eye care practitioners, but the medical community as a whole. Unfortunately, once the patient leaves the exam room, it is up to them to follow through with the treatment regimen. Providing substantial patient education has proven to be the best way to maintain effective medical therapy. While the science of drop comfort can help us to improve future pharmaceuticals, the doctor patient relationship is one of the most important initial steps in medical management. This research sought to uncover any tangible “rules” that could be transferred through patient education. As the medical field uncovers ways to combat disease unlike any other time in history, ensuring the most diligent patient compliance will be absolutely crucial to the success of the efforts of professionals across all medical disciplines.

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