Dilute Brimonidine to Improve Patient Comfort and Subconjunctival Hemorrhage After LASIK

Theodore A. Pasquali, MD; Adam Aufderheide, MD; Jason P. Brinton, MD; Michele R. Avila, OD; Erin D. Stahl, MD; Daniel S. Durrie, MD

ABSTRACT

PURPOSE: To investigate whether dilute brimonidine (0.025%) reduces patient discomfort, subconjunctival hemorrhage, and injection after LASIK without a significant increase in the rate of flap complications or surgical enhancements.

METHODS: This randomized, double-blind, prospective study enrolled 180 patients (360 eyes) in a contralateral eye comparison of topical dilute brimonidine, naphazoline/pheniramine, or Systane Ultra (Alcon Laboratories, Inc., Fort Worth, TX) administered shortly before LASIK for any indication. Patients were evaluated for subconjunctival hemorrhage, injection, and flap dislocation 1 hour and 1 day postoperatively. Patient questionnaires measuring patient comfort and ocular symptoms were administered at these same follow-up visits. Patients were examined for 3 months to determine similar outcomes for standard indices of safety, predictability, efficacy, and enhancement rates.

RESULTS: Scores of patient discomfort, subconjunctival hemorrhage, and injection were significantly lower in eyes treated with dilute brimonidine at the 1 hour and 1 day postoperative examinations. Refloats for mild-flap edge wrinkling were required in 3 brimonidine eyes (2.5%), 1 naphazoline/pheniramine eye (0.8%), and no control eyes, but this difference did not reach statistical significance ($P = .18$). There was no significant difference between eyes at 3 months in terms of visual acuity, refractive error, corrected distance visual acuity, or rate of enhancement.

CONCLUSIONS: Use of dilute brimonidine before LASIK reduces subconjunctival hemorrhage and injection and improves patient comfort after surgery. Flap edge wrinkling requiring refloat may still be a complication with dilute brimonidine.

[*J Refract Surg*. 2013;29(7):469-475.]

One of the reasons that LASIK has become the dominant refractive procedure is that it involves significantly less postoperative patient discomfort than other keratorefractive procedures.[1] Efforts have been made to improve comfort further, but they have not gained widespread adoption.[2,3] In our experience, one means of improving early postoperative patient comfort is the use of a single drop of dilute brimonidine (0.025%) prior to surgery.

Use of brimonidine before lamellar procedures has been studied for the reduction of subconjunctival hemorrhages that frequently occur due to the suction required for corneal applanation.[4] Although these hemorrhages are temporary and without significant visual consequence, reducing or eliminating them provides a more positive patient experience, avoids undue negative psychological effects, and enhances aesthetic outcomes in the procedure with a significant cosmetic component. Topical vasoconstrictors such as brimonidine,[5-8] apraclonidine,[9] phenylephrine,[10] or combined naphazoline/pheniramine eye drops[11] help reduce postoperative subconjunctival hemorrhage, injection, and hyperemia. However, the use of these medications has been avoided due to the possibility that they may increase the incidence of flap dislocations[8] and the frequency of surgical enhancements.[5] It remains controversial whether brimonidine increases the rate of flap dislocation; of two recent prospective contralateral eye studies investigating the use of brimonidine 0.2% before LASIK, one demonstrated no increase in flap dislocation and the other demonstrated a 10.4% increase in the rate of flap dislocation.[6,8] Another concern with the use of these medications is their effect on pupil size and shape,[12-14] which could potentially interfere with pupil tracking.

From Durrie Vision, Overland Park, Kansas (TAP, JPB, MRA, EDS, DSD); the Department of Ophthalmology, University of Kansas Medical Center, Kansas City, Kansas (AA, JPB, DSD); and Children's Mercy Hospitals and Clinics, Kansas City, Missouri (EDS).

Submitted: October 2, 2012; Accepted: March 12, 2013

Dr. Durrie is a consultant for Alcon Laboratories, Inc. and Abbott Medical Optics. The remaining authors have no proprietary or financial interest in the materials presented herein.

Correspondence: Daniel S. Durrie, MD, Durrie Vision, 5520 College Blvd., Suite 201, Overland Park, KS 66211. E-mail: ddurrie@durrievision.com

doi:10.3928/1081597X-20130617-05

In designing this study, we hypothesized that an optimal dilution of brimonidine could reduce the rate of complications associated with full dose brimonidine while maintaining the benefits. We present a prospective, randomized, double-blind study comparing 0.025% brimonidine, naphazoline/pheniramine, and control (artificial tears lubricant) to determine whether subconjunctival hemorrhage and injection can be minimized effectively without increasing the risks of flap dislocation or need for enhancement. In addition, we evaluated the validity of our observation that dilute brimonidine is effective in reducing patient discomfort in the first 24 hours after surgery, a finding that has not been previously reported.

PATIENTS AND METHODS

This prospective, randomized, double-blind, single-center clinical trial evaluated 180 patients (360 eyes) undergoing bilateral LASIK for refractive errors ranging from +6.00 to -12.00 diopters (D) sphere and up to -6.0 D of astigmatism. Inclusion criteria were a stable refraction for 1 year, an average central corneal thickness of at least 500 µm, and an otherwise healthy anterior segment. Written informed consent was obtained for all patients and the study was approved by an RCRC Independent Review Board.

Eligible patients were examined preoperatively for measurement of corrected and uncorrected distance and near vision, cycloplegic and manifest refraction, pachymetry, corneal topography, and slit-lamp and fundus examinations. Pupil diameter was measured under mesopic conditions using an infrared pupillometer (Neuroptics, Irvine, CA) during the preoperative visit. Postoperatively, patients underwent an ophthalmic evaluation at 1 hour, 1 day, 1 month, and 3 months. All eyes were assessed according to standard criteria for satisfactory LASIK outcomes related to safety, predictability, and efficacy. Each patient was asked to complete a subjective questionnaire 1 hour and 1 day postoperatively for self-evaluation of discomfort, irritation, burning, pain, and itching on a scale of 0 (none) to 7 (severe). Subconjunctival hemorrhage and injection were evaluated by slit lamp at 1 hour and 1 day postoperatively by a masked investigator using a grading scale of 0 (none) to 4 (severe) for each finding. Routine refraction and slit-lamp examinations were performed at the later postoperative visits.

Brimonidine tartrate ophthalmic solution 0.1% was compounded to 0.025% by an independent pharmacy in Overland Park, Kansas. Naphcon A (naphazoline hydrochloride 0.025%, pheniramine maleate 0.3%; Alcon Laboratories, Inc., Fort Worth, TX) and control (Systane Ultra, polyethylene glycol 400 0.4%, propylene glycol 0.3%; Alcon Laboratories, Inc.) are over-the-counter medications. All patients underwent bilateral surgery and were randomized to one of three regimens with 60 patients and 120 eyes each: (1) dilute brimonidine in one eye and control in the other eye, (2) naphazoline/pheniramine in one eye and control in the other eye, and (3) dilute brimonidine in one eye and naphazoline/pheniramine in the other eye. Five minutes prior to surgery, patients received one drop of the study medication according to the randomized group determination in addition to one drop of proparacaine and one drop of antibiotic.

A fourth-generation IntraLase FS Laser (60 kHz; Abbott Medical Optics, Santa Ana, CA) was used to create the LASIK flaps. Flap diameter was 8.5 mm and the intended flap thickness was 110 µm. A raster pattern was used with the hinge located in the superior position with raster energy of 1.2 mJ/spot and spot-line separation of 9 × 9 µm. The hinge angle was 50° and the side cut angle was 70° with pocket software enabled. Pupil size was measured under standardized light levels using the infrared pupillometer in the interim between flap creation and excimer ablation. All patients underwent vision correction performed with the same excimer laser (Allegretto Wave Eye-Q; WaveLight AG, Erlangen, Germany). All eyes received proparacaine 0.5% and tetracaine 0.5% drops during surgery. The goal of surgery was emmetropia or monovision of -0.75 to -1.50 depending on patient age and surgeon discretion.

Immediately after surgery, patients received a fourth generation fluoroquinolone antibiotic, prednisolone acetate 1%, and preservative-free artificial tears. Patients continued to use the antibiotic and steroid drops four times daily for 1 week and were encouraged to use the artificial tears frequently (every 15 to 30 minutes on the day of surgery, every 1 to 2 hours the day after surgery, tapering to six times daily with more frequent use if needed). Refloats were performed in a procedure room with sterile technique and a microscope with the patient in supine position. Determination of need for enhancement was made at the 3-month postoperative visit at the surgeon's discretion based on uncorrected vision and magnitude of refractive error. A data analysis software package (SAS, Cary, NC) was used to evaluate statistical significance. Results were analyzed by analysis of variance (ANOVA) with a Bonferroni correction test (alpha < .05, where alpha is a P value modified for multiple variable correction). The three treatment groups were also compared two by two (pairwise) to generate P values using the two-sample t test and P values were checked against the Bonferroni grouping to confirm agreement. Fisher exact test was used to calculate P val-

TABLE 1
Preoperative Patient Characteristics

Characteristics	Brimonidine	Naphazoline/Pheniramine	Control	*P* (BN, BC, NC)[a]
No. of eyes	120	120	120	
Gender				.24, .53, .58
Male	62	49	55	
Female	58	71	65	
Age (y)				
Mean ± SD	38.56 ± 10.64	38.06 ± 11	38.24 ± 10.38	.72, .81, .89
Range	20 to 59	20 to 60	20 to 60	
Sphere (D)				
Mean ± SD	-2.81 ± 3	-3.4 ± 2.44	-3.4 ± 2.44	.88, .10, .09
Range	-9.25 to 2.5	-9 to 3.5	-9 to 3.5	
Cylinder (D)				
Mean ± SD	-1.06 ± 1.14	-0.83 ± 0.83	-0.95 ± 0.94	.07, .38, .32
Range	-5.75 to 0	-5.5 to 0	-5.5 to 0	

BN = dilute brimonidine vs naphazoline/pheniramine; BC = dilute brimonidine vs control; NC = naphazoline/pheniramine vs control; SD = standard deviation; D = diopters
[a]*P values listed for the three* t *test pairwise comparisons.*

ues for flap dislocation rates (a categorical comparison). Using the reported rate of 1%[15,16] for the occurrence of flap dislocation in LASIK with femtosecond laser, power analysis determined that this study had 80% power to detect an increase of 0.06 (6%) in the rate of dislocation (GraphPad StatMate, San Diego, CA). Data are presented as mean ± standard deviation. *P* values less than .05 were considered significant.[15,16] Refractive outcome measures were calculated according to the standardized graphs as originally defined by Waring.[17]

RESULTS

The study included 360 eyes from 180 patients. There were no statistically significant differences between the groups in terms of preoperative characteristics (**Table 1**). One hundred sixty-two patients (90%) completed 3 months of follow-up examinations. All patients completed at least 1 day of follow-up, which was sufficient for inclusion in the analysis of flap dislocation, slit-lamp parameters (subconjunctival hemorrhage and injection), and patient questionnaires. However, only patients with 3 months of follow-up were able to be included in the analysis of visual outcomes and frequency of enhancements.

At 3 months, there were no significant differences between eyes in the percentage achieving 20/20 (logMAR 0.00) or better uncorrected visual acuity (for the respective target distance), mean spherical equivalent, mean absolute error, corrected distance visual acuity (CDVA), or in the enhancement rate (**Table 2**). Mean absolute error is calculated as the absolute value of the difference between the postoperative manifest refraction (spherical equivalent) and the target refraction. Refractive outcomes for each group are reported in **Figure 1**.

The use of dilute brimonidine or naphazoline/pheniramine significantly reduced the amount of injection and subconjunctival hemorrhage 1 hour postoperatively when compared to control (**Figure 2**), with dilute brimonidine demonstrating a greater amount of reduction than naphazoline/pheniramine ($P \leq .006$ for all pairwise comparisons for both parameters). In terms of incidence, only 10% of dilute brimonidine eyes were graded as having greater than "trace" subconjunctival hemorrhage versus 24% of the naphazoline/pheniramine eyes and 93% of control eyes. At the 1-day follow-up visit, dilute brimonidine and naphazoline/pheniramine continued to show a marked benefit in reducing subconjunctival hemorrhage when compared to control ($P < .001$ for both comparisons) (**Figure 2**), with dilute brimonidine exhibiting lower scores than naphazoline/pheniramine (0.17 ± 0.43 vs 0.34 ± .016, $P = .01$). However, by the 1-day follow-up visit, injection scores were no different between treatment groups (ANOVA $P = .32$ with $P \geq .16$ for all pairwise comparisons).

According to questionnaire responses, patients who received dilute brimonidine or naphazoline/pheniramine were markedly more comfortable and less symptomatic than those who received control 1 hour postoperatively in terms of discomfort, irritation, burning, pain, and itching scores ($P < .01$ for all symptom score comparisons), whereas scores for dilute brimonidine and naphazoline/pheniramine were not statistically different

TABLE 2
Surgical Outcomes at 3 Months

Characteristic	Brimonidine	Naphazoline/Pheniramine	Control	*P* (BN, BC, NC)[a]
No. of eyes	108	107	108	
UDVA (logMAR) for distance corrected eyes				
No.	81	87	82	
Mean ± SD	-0.07 ± 0.12	-0.06 ± 0.12	-0.07 ± 0.12	.54, .83, .40
Range	-0.30 to 0.30	-0.30 to 0.40	-0.30 to 0.40	
UNVA (logMAR) for near corrected eyes				
No.	27	20	26	
Mean ± SD	0.07 ± 0.13	0.08 ± 0.16	0.07 ± 0.11	.82, .88, .72
Range	-0.10 to 0.40	-0.20 to 0.40	-0.10 to 0.30	
MAE (D)				
Mean ± SD	0.24 ± 0.25	0.29 ± 0.30	0.28 ± 0.30	.26, .36, .84
Range	0 to 1.38	0 to 1.88	0 to 1.50	
CDVA (D)				
Mean ± SD	-0.10 ± 0.09	-0.11 ± 0.08	-0.10 ± 0.08	.80, .87, .66
Range	-0.30 to 0.20	-0.30 to 0.20	-0.30 to 0.20	
Enhancements (eyes)	8 (7.4%)	9 (8.4%)	8 (7.4%)	.80, 1.0, .80

BN = dilute brimonidine vs naphazoline/pheniramine; BC = dilute brimonidine vs control; NC = naphazoline/pheniramine vs control; UDVA = uncorrected distance visual acuity; SD = standard deviation; UNVA = uncorrected near visual acuity; MAE = mean absolute error; D = diopters; CDVA = corrected distance visual acuity

[a]*P values listed for the three* t *test pairwise comparisons.*

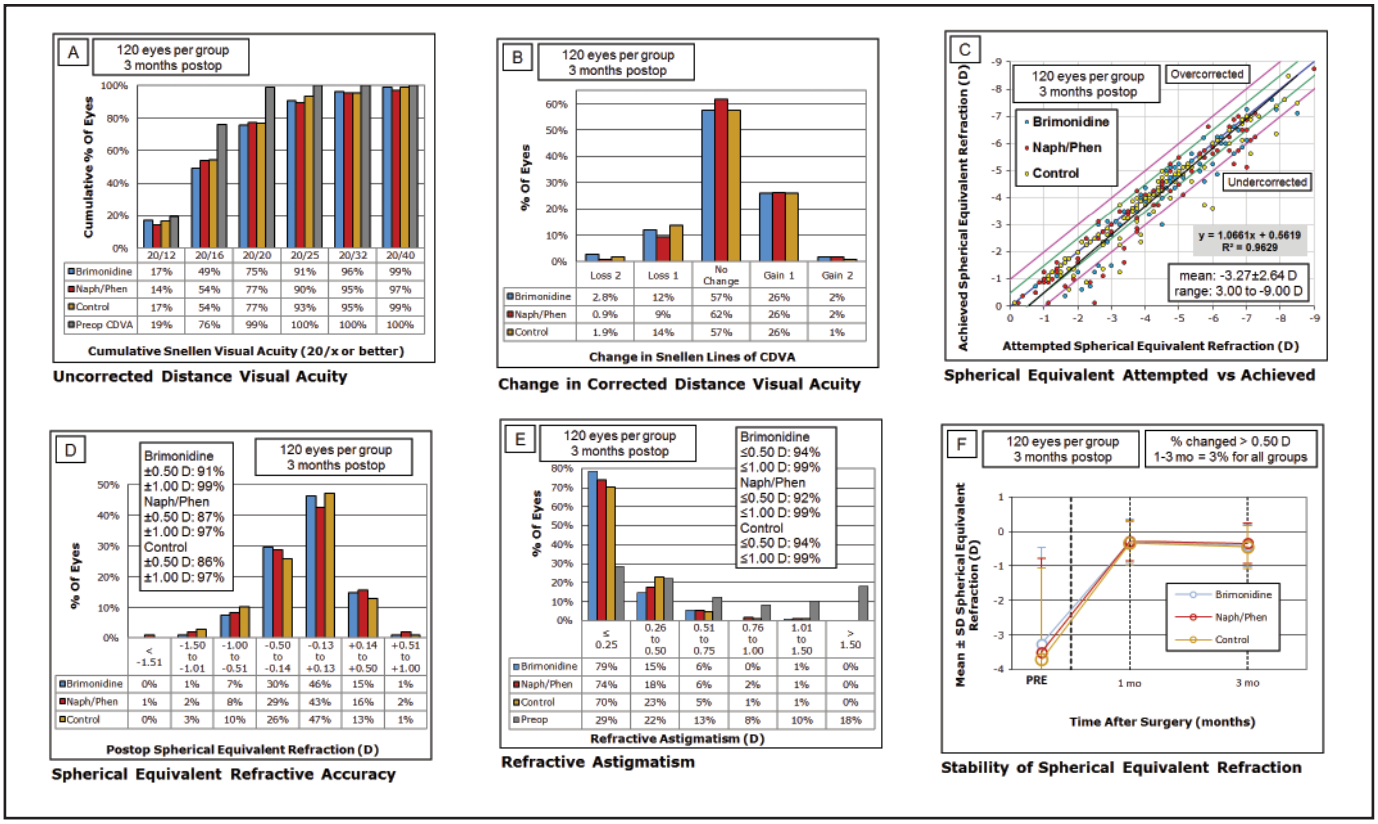

Figure 1. The standard graphs for reporting refractive surgery adapted to present the outcomes for the three groups.

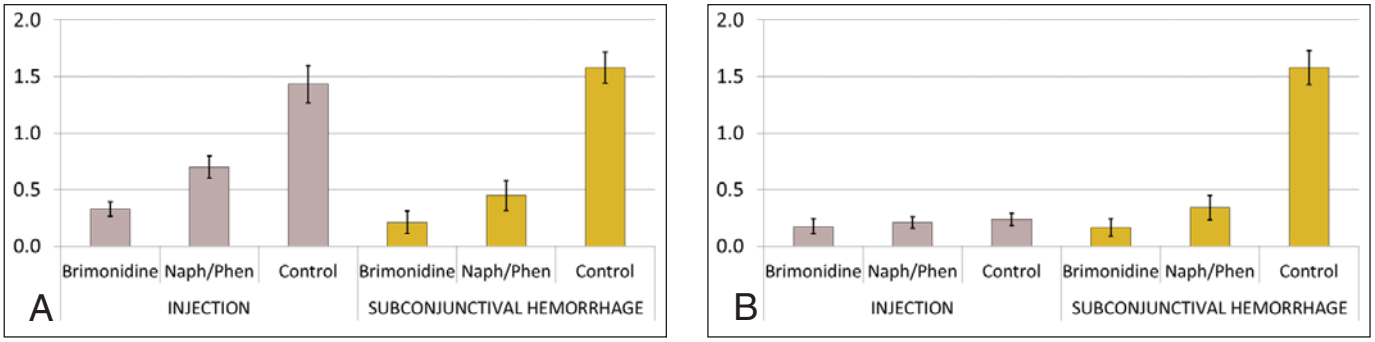

Figure 2. Slit-lamp findings (A) 1 hour and (B) 1 day postoperatively for each medication. Error bars represent confidence intervals. The Y axis values represent the graded scoring system, 0 for no findings and 4 for severe. Naph/Phen = naphazoline/pheniramine

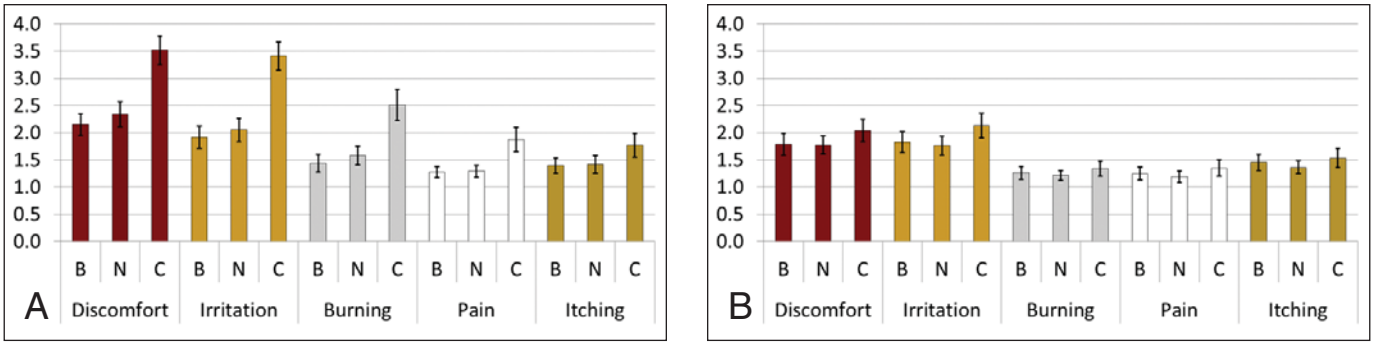

Figure 3. Questionnaire results (A) 1 hour and (B) 1 day postoperatively. The Y axis values represent the patient response scoring scale, where 1 represents most comfort/no symptoms and 7 represents most discomfort/worst symptoms. B = dilute brimonidine, N = naphazoline/pheniramine, C = control

($P > .23$ for all symptom score comparisons). One day postoperatively, symptom scores for discomfort, burning, pain, and itching (**Figure 3**) were statistically similar for the three treatment groups (ANOVA $P > .09$ for these four symptoms). Irritation scores 1 day postoperatively for eyes treated with control were significantly higher when compared to scores for dilute brimonidine eyes ($P = .047$) and naphazoline/pheniramine eyes ($P = .01$); however, there was no difference between dilute brimonidine and naphazoline/pheniramine treatments ($P = .63$).

Mild-flap edge wrinkling occurred in three (2.5%) of the dilute brimonidine eyes and one (0.8%) of the naphazoline/pheniramine eyes with no instances (0%) in the control group. This difference did not reach statistical significance ($P = .18$, Fisher exact test). Two eyes were refloated at 1 day and two eyes at 1 hour. No eyes experienced flap dislocations.

The 3-month outcomes for the four eyes requiring refloat due to flap wrinkling are presented in **Table 3**. All four eyes had 20/25 or better visual acuity and all corrected eyes had 20/20 or better visual acuity at their last follow-up visit with no loss of CDVA. None of the eyes demonstrated more than 0.50 D difference in sphere or cylinder between the target and achieved refractive outcome. One additional refloat was performed 5 days postoperatively due to diffuse lamellar keratitis in a naphazoline/pheniramine group eye. The diffuse lamellar keratitis was likely related to an epithelial defect that developed after surgery unrelated to the study medication. The refloat was not included in the analysis because it was not related to flap dislocation or wrinkling.

TABLE 3

Outcomes at 3 Months of Patients With Mild Flap Edge Wrinkling Successfully Refloated

Medication	UDVA	Sphere	Cylinder	CDVA
Nephazoline/pheniramine	20/20	0.50	0.00	20/20
Brimonidine	20/20	-0.25	-0.25	20/20
Brimonidine	20/20	0.00	0.00	20/20
Brimonidine	20/25	-0.50	0.00	20/20

UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity.
Visual acuity is in Snellen equivalent.

There were no instances of pupil size adversely affecting the ability of the laser software to accurately track pupil locations during the treatment in any of the eyes.

DISCUSSION

It is believed that brimonidine can destabilize flap adherence by adversely affecting corneal reepithe-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.