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Epidemiology of persistent post-surgical pain manifesting as dry eye-like symptoms after cataract surgery

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Abstract

Purpose: To evaluate the epidemiology of persistent post-surgical pain (PPP) manifesting as dry eye (DE)-like symptoms 6 months after surgery.

Methods: The single-center study population included 119 individuals whose cataract surgeries were performed by a single surgeon at the Bascom Palmer Eye Institute and who agreed to participate in a phone survey six months after surgery. Patients were divided into two groups: PPP group was defined as those with a Dry Eye Questionnaire-5 (DEQ5) score ≥ 6 and without PPP (WoPPP) as those with DEQ5 score < 6 at six months after cataract surgery.

Results: The mean age of the study population was 73 ± 8.0 years; 55% ($n=66$) were female. PPP was present in 34% ($n=41$) of individuals six months after surgery. Factors associated with an increased risk of PPP were female gender (Odds ratio (OR)=2.68, 95% confidence interval (CI)=1.20–6.00, $p=0.01$), autoimmune disorder (OR=13.2, CI=1.53–114, $p=0.007$), non-ocular chronic pain disorder (OR=4.29, CI=1.01–18.1, $p=0.06$), antihistamine use (OR=6.22, CI=2.17–17.8, $p=0.0003$), anti-reflux medication use (OR=2.42, CI=1.04–5.66, $p=0.04$), antidepressant use (OR=3.17, CI=1.31–7.68, $p=0.01$), anxiolytic use (OR=3.38, CI=1.11–10.3, $p=0.03$), and anti-insomnia medication use (OR=5.28, CI=0.98–28.5, $p=0.047$). PPP patients also reported more frequent artificial tears use ($p<0.0001$), higher ocular pain levels ($p<0.0001$), and greater

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neuropathic ocular pain symptoms, including burning ($p=0.001$), wind sensitivity ($p=0.001$), and light sensitivity ($p<0.0001$).

Conclusions: PPP in the form of persistent dry eye-like symptoms is present in approximately 34% of individuals six months after cataract surgery. The frequency of PPP after cataract surgery is comparable with that of other surgeries including laser refractive surgery, dental implants, and genitourinary procedures.

Keywords

cataract surgery; dry eye symptoms; persistent post-surgical pain; epidemiology

INTRODUCTION

Dry eye (DE) symptoms are common and experienced by 5% to over 35% of individuals across various age groups.¹ These symptoms can be painful and debilitating, significantly affecting productivity and quality of life.² Therefore, patients stand to benefit from adequate management of their symptoms, but clinical determination of treatment adequacy can be challenging, as signs and symptoms of DE are often discordant.³ There is a growing understanding that this discrepancy may, in part, be explained by nerve injury and pathologic neuroplasticity underlying persistent and often severe DE symptoms.⁴⁻⁶

Many symptoms of DE are typical of other neuropathic pain syndromes. These symptoms have been termed neuropathic ocular pain (NOP) and include burning, hypersensitivity to wind, photoallodynia (abnormal light sensitivity), and reduced mechanical pain thresholds.^{6, 7} Moreover, NOP symptoms have been associated with an incomplete response to treatment with artificial tears⁸ and with somatosensory dysfunction remote from the eye.⁹ NOP and non-ocular chronic pain syndromes are often comorbid and the emerging concept termed Chronic Overlapping Pain Conditions (COPC) suggests shared mechanisms within susceptible patients.^{10, 11} Indeed, a history of COPC is associated with an increased risk for concomitant DE symptoms.¹²

Surgical nerve injury can result in pathologic neuroplasticity in susceptible individuals which can lead to persistent post-surgical pain (PPP).⁵ To be considered PPP, the pain should follow surgery and persist for three to six months after tissue healing.^{13, 14} PPP occurs in roughly 10–50% of patients, but its incidence and associated risk factors vary greatly by surgical procedure.¹⁵ Breast surgery, coronary artery bypass surgery, and thoracotomy have incidences as high as 40–70%, whereas cesarean section, dental implant surgery, and inguinal hernia repair have incidences closer to 10–30%.^{13, 14, 16} Common identified risk factors include comorbid chronic pain disorders, anxiety, depression, younger age, family history, preoperative pain, acute postoperative pain, and repeat surgery.^{15, 17, 18} Considering that the cornea is among the most densely innervated tissues in the body,⁴ it is plausible that PPP occurs after ocular procedures, such as cataract surgery. However, the epidemiology of PPP after cataract surgery has not been well studied.

Based on the International Association for the Study of Pain classifications, some DE symptoms meet the definition of pain¹⁹ and thus, persistent DE symptoms after cataract

surgery may represent PPP in the eye.²⁰ Several studies have evaluated the frequency of DE symptoms up to three months postoperatively, but this time period may still encompass tissue healing and thus does not meet the definition of chronicity.¹³ This study seeks to fill the knowledge gap regarding PPP epidemiology after ocular surgery by ascertaining the prevalence of post-operative DE symptoms 6 months after cataract surgery, including NOP symptoms, and identifying risk factors for PPP.

METHODS

Study population:

A retrospective chart review identified 201 patients who underwent cataract surgery performed by a single surgeon using standard phacoemulsification technique with clear corneal incisions between January 10, 2016 and January 9, 2017 at Bascom Palmer Eye Institute in Naples, Florida. No concomitant procedures were performed at the time of cataract surgery. Of this cohort, 119 patients agreed to participate in a phone-administered standardized questionnaire, which was conducted approximately five to seven months after their cataract surgery. Of these, 56 had undergone cataract surgery in 1 eye and 63 in both eyes.

Ocular surface optimization was performed preoperatively for patients experiencing DE symptoms and for patients whose ocular surface was compromised enough to impact corneal keratometry or tomographic measurements. This included a combination of non-preserved artificial tears, cyclosporine, and punctal plugs as needed per patient requirements, until symptoms were under control, and tomographic measurements were improved and stable.

The standard perioperative regimen was a compounded single vial of prednisolone, gatifloxacin, and nepafenac 4 times/day starting 2 days prior to surgery and continuing for one week after surgery. A second bottle, compounded with prednisolone and nepafenac 3 times/day, was started 7 days after surgery and tapered by 1 drop each week for three weeks. The standard surgical technique consisted of a 2.5 mm temporal clear corneal incision and a 1.0 mm paracentesis. The University of Miami Institutional Review Board (IRB) permitted phone-based survey administration and retrospective review of patient records. The study was conducted in accordance with the principles of the Declaration of Helsinki and Declaration of the World Medical Association.

Data collection:

Information was gathered through comprehensive chart reviews and a standardized questionnaire conducted over the phone. Information obtained from chart reviews included patients' demographics, preoperative nuclear sclerotic cataract grade, best corrected postoperative visual acuity, intraoperative complications, medications, and medical comorbidities. Where relevant, medications and comorbidities were grouped into meaningful categories (e.g. anxiolytics, non-ocular chronic pain disorders).

The standardized questionnaire (Supplemental Digital Content (SDC) Table 1) employed in the phone interviews assessed the presence of preoperative and postoperative DE symptoms and quantified current DE symptomatology using the validated Dry Eye Questionnaire-5

(DEQ5).²¹ Current overall ocular pain and specific NOP symptoms were also solicited and quantified²² using a numerical rating scale (NRS) of 0–10. The final question assessed acute postoperative pain, a previously reported risk factor for developing PPP, using an NRS. A 0–10 NRS was chosen as the assessment tool as it has been demonstrated across multiple populations to be a valid measure of pain intensity and has been recommended as the primary outcome metric in chronic pain clinical trials.²³ If a patient underwent cataract surgery in both eyes 6 months prior to participation in the phone survey, survey responses were solicited for both eyes and the worse/higher of the responses were used for statistical calculations.

Patients were divided into PPP and WoPPP (without PPP) based on their total DEQ5 score. The PPP group was defined as those with a DEQ5 score ≥ 6 , while the WoPPP group was defined as those with DEQ5 score < 6 at six months after cataract surgery. As a subgroup, patients with DEQ5 score ≥ 12 were defined as having severe PPP (SPPP).

Outcomes:

In designing the study, we chose the DEQ5 score 6 months after cataract surgery as a measure of PPP as it is a validated tool for the assessment of DE symptoms and less subject to recall bias. Primary outcomes included the prevalence of PPP (DEQ5 ≥ 6) and SPPP (DEQ5 ≥ 12) and their associated risk factors. As this PPP definition encompasses individuals with chronic persistent symptoms as well as those who developed new symptoms, as a secondary outcome, we examined DE symptom course (the development of new or the persistence of chronic DE symptoms postoperatively) using a methodology similar to other PPP studies.²⁴ Logistic regression analysis was conducted to determine statistical significance, and all statistical analyses were performed using the SPSS 22.0 (SPSS Inc, Chicago, IL) statistical package.

RESULTS

Demographics of the study population and frequency of PPP:

The study population consisted of 53 male (45%) and 66 female patients (55%), and mean age was 73 (standard deviation (SD) 8.0). Race was available for 89% and ethnicity for 92% of the study population. The majority were white (95%) and non-Hispanic (97%). Hispanic individuals were less likely to participate in the phone interview. Otherwise, there were no significant differences in demographics, best corrected postoperative visual acuity, medical comorbidities, or medication use between those who did and did not participate in the phone interview. Based on results of the DEQ5, there were 41 individuals with PPP and 78 individuals without PPP. Thus, the frequency of PPP in our population was 34%. The frequency of severe PPP was 18% (n=22). Female gender was associated with an increased risk of PPP (odds ratio (OR)=2.68; 95% confidence interval (CI)=1.20–6.00; p=0.01). (Table 1)

Medical comorbidities and medications and their relation to PPP:

Most medical comorbidities (Table 1) and medications (Table 2) were not associated with an increased risk of PPP. Notably however, the presence of an autoimmune disease (i.e.

rheumatoid arthritis, systemic lupus erythematosus, Sjögrens, polymyalgia rheumatica, and/or multiple sclerosis) conferred an increased risk of PPP (OR=13.2; 95% CI=1.53–114; p=0.007) as did the presence of a non-ocular chronic pain disorder (i.e. headache, migraine, low back pain, and/or fibromyalgia) (OR=4.29; 95% CI=1.01–18.1; p=0.06). Not surprisingly, a prior documented diagnosis of DE was associated with an increased risk of PPP (OR=3.90; 95% CI=1.59–9.54; p=0.003).

Medications that were significantly associated with PPP included antihistamines (OR=6.22, 95% CI=2.17–17.8; p=0.0003), anti-reflux medications (i.e. proton pump inhibitors or antacids) (OR=2.42; 95% CI=1.04–5.66; p=0.04), antidepressants (OR=3.17; 95% CI=1.31–7.68; p=0.01), anxiolytics (OR=3.38; 95% CI=1.11–10.3; p=0.03), and anti-insomnia medications (OR=5.28; 95% CI=0.98–28.5; p=0.047). In a multivariable analysis, autoimmune disease (OR=10.1; 95% CI=1.07–96.4; p=0.04), antihistamine use (OR=6.73; 95% CI=2.23–20.4; p=0.001), and antidepressant use (OR=2.97; 95% CI=1.12–7.90; p=0.03) remained significantly associated with PPP.

Significant risk factors for severe PPP included autoimmune comorbidity (OR=6.96; 95% CI=1.44–33.8; p=0.02) and anti-insomnia medications (OR=6.96; 95% CI=1.44–33.8; p=0.02) (Table 3).

Ocular pain, artificial tear use, and symptom course and their relation to PPP:

Patients with PPP reported higher ocular pain over a 1-week recall compared to those WoPPP (1.73, SD 2.2 vs 0.15, SD 0.7; p<0.0001) (Table 4), and they reported higher levels of NOP, specifically spontaneous burning pain (1.15, SD 2.0 vs 0.04, SD 0.3; p=0.001), sensitivity to wind (1.56, SD 2.6 vs 0.15, SD 0.6; p=0.001), and sensitivity to light (3.51, SD 3.5 vs 0.85, SD 1.9; p<0.0001). PPP patients also used artificial tears more frequently than controls (2.05, SD 1.9 vs 0.24, SD 0.6; p<0.0001).

Regarding the course of DE symptoms, prior to cataract surgery, 74 patients recalled having no DE symptoms while 45 reported having pre-existing DE symptoms. Of the 74 individuals without a history of DE symptoms, 14 (19%) reported new symptoms. Of the 45 individuals with pre-existing symptoms, 34 (76%) reported stable or improved symptoms while 11 (24%) reported worse symptoms. PPP patients also recalled a higher level of acute postoperative pain compared to those WoPPP during the first postoperative week (1.61, SD 2.7 vs 0.51, SD 1.5; p=0.02) which was a risk for PPP (OR=1.30; 95% CI=1.06–1.60). Considering only individuals without a preoperative history of DE symptoms, anti-reflux medication (OR=3.57; 95% CI=1.13–11.2; p=0.02) and non-ocular chronic pain disorder (OR=4.50; 95% CI=0.99–20.6; p=0.07) increased the risk of new, persistent DE symptoms after surgery.

Preoperative cataract grade and intraoperative complications and their relation to PPP:

Preoperative nuclear sclerotic cataract grade was similar between the PPP and WoPPP groups (2.27, SD 0.7 vs 2.28, SD 0.7), and a higher cataract grade did not confer an increased risk of PPP (OR=0.97; 95% CI=0.55–1.71; p=0.92). Three intraoperative complications were identified: one anterior capsular tear and two cases of vitreous loss which necessitated placement of an anterior chamber intraocular lens. The presence of an

intraoperative complication did not increase the risk for PPP (OR=0.95; 95%CI=0.08–10.8; p=1.00). (Table 1)

DISCUSSION

To conclude, we found an overall PPP prevalence of 34% and severe PPP prevalence of 18% six months after cataract surgery. Symptoms of NOP (spontaneous burning and wind/light sensitivity) were significantly more prevalent among those with PPP compared to those WoPPP. Several risk factors were identified for PPP after cataract surgery, namely female gender, autoimmune comorbidity, and pre-existing non-ocular chronic pain conditions. In addition, we found that certain medications were associated with increased risk of PPP including antihistamines, anti-reflux medications, antidepressants, anxiolytics, and anti-insomnia treatments.

In the context of existing PPP literature, the frequency quantified in this study is comparable to those of dental implant surgery (8.5–36%)¹⁶ and inguinal hernia repair (5–30%).¹³ It may also overlap with frequencies seen in procedures often considered high-risk for PPP such as thoracotomy (5–65%),¹³ breast surgery (20–50%),¹³ and coronary artery bypass surgery (44%),¹³ suggesting that cataract surgery be classified as a medium-risk procedure. Our frequency of PPP after cataract surgery is also similar to the incidence of new DE symptoms reported 6 months after LASIK surgery (19.5%).²⁵ Our study corroborated previously reported PPP risk factors such as autoimmune comorbidity,²⁶ female gender,¹⁸ acute postoperative pain,¹⁸ chronic pain disorders,^{15, 17} and, indirectly by way of medication usage, anxiety and depression.¹⁵ Also in concordance with previous literature, PPP patients experienced higher levels of NOP symptoms⁷ even though they used artificial tears more frequently.⁸ We were unable to confirm younger age as a risk factor,^{15, 17, 18} due to the predominantly older age of the study population. Interestingly, use of AREDS/Lutein appeared protective against PPP, a benefit that may be due to the antioxidant ingredients in these formulations.^{27, 28}

DE symptoms are classically thought to arise due to a disturbance in either the tear film or the orbital structures that give rise to or interact with the tear film, but recent consensus has highlighted a concomitant role of neurogenic stress and ocular surface inflammation.²⁹ The dense innervation of the cornea and the known corneal nerve injury that occurs at surgical incision likely form the backdrop for the development of PPP after cataract surgery.⁴ Of the corneal sensory fibers, 70% are polymodal nociceptors that respond to near-noxious mechanical forces, heat, chemical irritants, and numerous endogenous metabolites and cytokines.⁴ Injury to these nerve fibers triggers neurogenic inflammation that may gradually resolve or lead to pathologic neuroplasticity, a phenomenon associated with lowered stimulation thresholds, enhanced responses to stimulation, and spontaneous neurosensory firing, which can manifest as spontaneous pain and hyperalgesia.⁴ These changes associated with peripheral and central somatosensory sensitization may contribute to symptom severity and chronicity.¹⁴ The risk factors associated with PPP may impact predisposition to these maladaptive neurosensory changes, and further work is needed to identify and characterize those genetic and environmental factors underlying PPP after cataract surgery.

Given what we have learned about PPP prevention in high-risk surgical procedures, symptom management after cataract surgery may focus on three major objectives: 1) minimizing ocular surface nerve damage by careful surgical dissection; 2) pre-surgical treatment of modifiable comorbid risk factors (e.g. anxiety); and 3) perioperative pain control.¹⁴ For the prevention of acute postoperative pain, our patients received drops containing corticosteroid and nonsteroidal anti-inflammatory drug (NSAID), both of which have been used in multimodal analgesia regimens to minimize PPP after other surgical procedures.³⁰ Other analgesic medications that have been studied in postoperative patients include calcium channel alpha 2 delta ligands (i.e. gabapentin, pregabalin), which have shown promise in preventing PPP,^{13, 14, 17, 30} and ketamine, which was found on meta-analysis to decrease the incidence of PPP although with small ketamine treatment arms in most studies (n<100).³¹ Future investigations may elucidate the true benefit of agents such as gabapentin and ketamine in the prevention of PPP after cataract surgery.

Our conclusions must be understood in the context of this study's definitions and limitations. We defined PPP after cataract surgery as a DEQ5 score ≥ 6 at six months after cataract surgery. As discussed above, this definition encompasses patients who developed new symptoms as well as those with pre-existing chronic symptoms. Therefore, patients were additionally asked about the course of their symptoms (new or worse) which is subject to recall bias. Since our study did not include a preoperative symptom assessment, we are unable to definitively quantify symptom development or progression but rather have a snapshot of DE symptoms experienced six months after cataract surgery. Moreover, many of our medication-based and comorbidity-based subgroups contained fewer than five patients, under-powering the ability to evaluate these individual categories. Similarly, the low number of intraoperative complications in this sample does not allow us to adequately assess their impact on PPP. Another limitation of our study is that we did not have information on phacoemulsification energy used at the time of surgery and can thus not comment on its correlation with dry eye-like symptoms severity. However, it is encouraging that preoperative cataract grade was not a risk factor for PPP. Lastly, as many patients chose not to participate in the phone survey or could not be reached, an element of selection bias may be present. Nonetheless, this study identifies that PPP is present in a significant subset of patients after cataract surgery, and the observed frequency of PPP is comparable with other surgical procedures. Future studies with larger patient cohorts and prospective methodology will be worthwhile to validate and extend our findings. Additionally, lessons learned about the prevention and treatment of PPP in other studies may serve as a guide to test new strategies in addressing PPP after cataract surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Demographics and medical comorbidities of the study population and their association with persistent post-surgical pain after cataract surgery (defined as a Dry Eye Questionnaire-5 score of 6 or greater)

	PPP (n=41)	WoPPP (n=78)	Odds ratio	95% CI	P-value
Demographic					
Age, mean (SD)	72 (7.8)	73 (8.1)	0.99	0.94–1.04	0.67
Gender, n (%) female, female/male	29 (71%)	37 (47%)	2.68	1.20–6.00	0.01
Race, n (%) non-white, non-white/white	2 (6%)	4 (6%)	0.96	0.17–5.49	1.00
Ethnicity, n (%) Hispanic (H), H/non-H	1 (3%)	3 (4%)	0.60	0.06–6.01	1.00
Systemic					
			yes/no		
Cancer, n (%)	8 (20%)	13 (17%)	1.21	0.46–3.21	0.70
Cataract Grade					
Preoperative nuclear sclerotic cataract grade, mean (SD)	2.27 (0.7)	2.28 (0.7)	0.97	0.55–1.71	0.92
Ocular					
			yes/no		
Intraoperative complications, n (%)	1 (2%)	2 (3%)	0.95	0.08–10.8	1.00
Corneal pathology (keratoconus, endothelial dystrophy), n (%)	4 (10%)	4 (5%)	2.00	0.47–8.45	0.44
Physician diagnosis of DE prior to surgery, n (%)	16 (39%)	11 (14%)	3.90	1.59–9.54	0.003
Lid margin disease (MGD, blepharitis), n (%)	2 (5%)	6 (8%)	0.62	0.12–3.20	0.71
Glaucoma, n (%)	8 (20%)	11 (14%)	1.48	0.54–4.02	0.45
Retinal pathology (MD, RD, macular hole, CNVM, CSR, ERM, CME), n (%)	14 (34%)	38 (49%)	0.55	0.25–1.20	0.13
Vascular					
Hypertension, n (%)	20 (49%)	35 (45%)	1.17	0.55–2.50	0.69
Diabetes mellitus, n (%)	7 (17%)	15 (19%)	0.87	0.32–2.33	0.77
Dyslipidemia, n (%)	6 (15%)	11 (14%)	1.04	0.36–3.06	0.94
Respiratory					
Obstructive sleep apnea, n (%)	3 (7%)	1 (1%)	6.08	0.61–60.4	0.12
Asthma/COPD, n (%)	5 (12%)	6 (8%)	1.67	0.48–5.83	0.51
Gastrointestinal					
GERD, n (%)	8 (20%)	8 (10%)	2.12	0.73–6.15	0.17
Psychiatric					
Depression, n (%)	1 (2%)	1 (1%)	1.93	0.12–31.6	1.00
Anxiety, n (%)	1 (2%)	2 (3%)	0.95	0.08–10.8	1.00
Neurologic					
Non-ocular chronic pain (headache, migraine, low back pain, fibromyalgia), n (%)	6 (15%)	3 (4%)	4.29	1.01–18.1	0.06
Rheumatologic					
Arthritis, n (%)	9 (22%)	13 (17%)	1.41	0.54–3.63	0.49
Gout, n (%)	2 (5%)	2 (3%)	1.95	0.26–14.4	0.61
PMR, n (%)	2 (5%)	0 (0%)	NC	NC	0.12
Any autoimmune condition (RA/SLE/Sjögrens/PMR/MS), n (%)	6 (15%)	1 (1%)	13.2	1.53–114	0.007

PPP: Persistent Post-surgical Pain, WoPPP: Without Persistent Post-surgical Pain, SD: Standard Deviation, CI: Confidence Interval, NC: Not Calculable, DE: Dry Eye, MGD: Meibomian Gland Dysfunction, MD: Macular Degeneration, RD: Retinal Detachment, CNVM: Choroidal Neovascular Membrane, CSR: Central Serous Retinopathy, ERM: Epiretinal Membrane, CME: Cystoid Macular Edema, COPD: Chronic Obstructive Pulmonary Disease, GERD: Gastroesophageal Reflux Disease, PMR: Polymyalgia Rheumatica, RA: Rheumatoid Arthritis, SLE: Systemic Lupus Erythematosus, MS: Multiple Sclerosis

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Table 2:

Medications used by the study population and their association with persistent post-surgical pain after cataract surgery (defined as a Dry Eye Questionnaire-5 score of 6 or greater)

	PPP (n=41)	WoPPP (n=78)	Odds ratio (yes/no)	95% CI	P-value
Systemic					
Antihistamine, n (%)	14 (34%)	6 (8%)	6.22	2.17–17.8	0.0003
Analgesic (opioids, acetaminophen, NSAID), n (%)	12 (29%)	16 (21%)	1.60	0.67–3.82	0.29
Ocular					
Artificial tears on record, n (%)	7 (17%)	2 (3%)	7.82	1.54–39.6	0.008
Lifitegrast/cyclosporine, n (%)	6 (15%)	2 (3%)	6.51	1.25–33.9	0.02
Glaucoma medications, n (%)	8 (20%)	10 (13%)	1.65	0.60–4.56	0.34
Immunomodulator (oral or topical), n (%)	12 (29%)	11 (14%)	2.52	1.00–6.37	0.051
AREDS/Lutein, n (%)	1 (2%)	15 (19%)	0.11	0.01–0.83	0.01
Vascular					
Antihypertensive, n (%)	25 (61%)	43 (55%)	1.27	0.59–2.75	0.54
Diabetes medications, n (%)	6 (15%)	12 (15%)	0.94	0.33–2.73	0.91
Lipid lowering agents, n (%)	21 (51%)	41 (53%)	0.95	0.45–2.02	0.89
Antiplatelet, n (%)	16 (39%)	30 (39%)	1.02	0.47–2.22	0.95
Anticoagulants, n (%)	3 (7%)	6 (8%)	0.95	0.22–4.00	1.00
Respiratory					
Inhaler, n (%)	10 (24%)	11 (14%)	1.97	0.76–5.11	0.17
Montelukast, n (%)	3 (7%)	3 (4%)	1.97	0.38–10.2	0.41
Gastrointestinal					
Anti-reflux (PPI, antacid), n (%)	15 (37%)	15 (19%)	2.42	1.04–5.66	0.04
Psychiatric					
Antidepressant, n (%)	15 (37%)	12 (15%)	3.17	1.31–7.68	0.01
Anxiolytic, n (%)	9 (22%)	6 (8%)	3.38	1.11–10.3	0.03
Anti-insomnia, n (%)	5 (12%)	2 (3%)	5.28	0.98–28.5	0.047
Neurologic					
Calcium channel alpha 2 delta ligands (gabapentin, pregabalin), n (%)	10 (24%)	2 (3%)	12.3	2.54–59.2	0.0004
Antiepileptic, n (%)	1 (2%)	3 (4%)	0.63	0.06–6.21	1.00
Rheumatologic					
Anti-gout, n (%)	2 (5%)	3 (4%)	1.28	0.21–8.00	1.00
Endocrine					
Thyroid replacement, n (%)	9 (22%)	16 (21%)	1.09	0.43–2.74	0.86
HRT, n (%)	3 (7%)	4 (5%)	1.46	0.31–6.86	0.69

PPP: Persistent Post-surgical Pain, WoPPP: Without Persistent Post-surgical Pain, CI: Confidence Interval, NSAID: Non-Steroidal Anti-Inflammatory Drugs, AREDS: Age Related Eye Disease Study, PPI: Proton Pump Inhibitor, HRT: Hormone Replacement Therapy

Table 3:

Medical comorbidities and medications notably associated with severe persistent post-surgical pain after cataract surgery (defined as a Dry Eye Questionnaire-5 score of 12 or greater)

	SPPP (n=22)	Wo SPPP (n=97)	Odds ratio	95% CI	P-value
Demographic					
Gender, n (%) female, female/male	16 (73%)	50 (52%)	2.51	0.91–6.95	0.07
Neurologic			yes/no		
Non-ocular chronic pain (headache, migraine, low back pain, fibromyalgia), n (%)	4 (18%)	5 (5%)	4.09	1.00–16.7	0.06
Rheumatologic					
Sjögrens, n (%)	2 (9%)	0 (0%)	NC	NC	0.03
Any autoimmune condition (RA/SLE/Sjögrens/PMR/MS), n (%)	4 (18%)	3 (3%)	6.96	1.44–33.8	0.02
Ocular					
Artificial tears on record, n (%)	6 (27%)	3 (3%)	11.8	2.67–51.8	0.001
Lifitegrast/cyclosporine, n (%)	4 (18%)	4 (4%)	5.17	1.18–22.6	0.04
Psychiatric					
Anti-depressant, n (%)	8 (36%)	19 (20%)	2.35	0.86–6.40	0.10
Anxiolytic, n (%)	5 (23%)	10 (10%)	2.56	0.78–8.43	0.15
Anti-insomnia, n (%)	4 (18%)	3 (3%)	6.96	1.44–33.8	0.02

SPPP: Severe Persistent Post-surgical Pain, WoSPPP: Without Severe Persistent Post-surgical Pain, NC: Not Calculable, PMR: Polymyalgia Rheumatica, RA: Rheumatoid Arthritis, SLE: Systemic Lupus Erythematosus, MS: Multiple Sclerosis

Table 4:

Ocular pain symptoms and artificial tear use reported by those with persistent post-surgical pain after cataract surgery (defined as a Dry Eye Questionnaire-5 score of 6 or greater) and those without

	PPP (n=41)	WoPPP (n=78)	P-value
Average ocular pain over 1 week recall in (worse) operated eye, mean (SD)	1.73 (2.2)	0.15 (0.7)	<0.0005
Spontaneous ocular burning in (worse) operated eye, mean (SD)	1.15 (2.0)	0.04 (0.3)	0.001
Sensitivity to wind, mean (SD)	1.56 (2.6)	0.15 (0.6)	0.001
Sensitivity to light, mean (SD)	3.51 (3.5)	0.85 (1.9)	<0.0005
Uses of artificial tears per day, mean (SD)	2.05 (1.9)	0.24 (0.6)	<0.0005

PPP: Persistent Post-surgical Pain, WoPPP: Without Persistent Post-surgical Pain, SD: Standard Deviation