BMJ Open

Pain related to intravitreal injections for age-related macular degeneration: a qualitative study of the perspectives of patients and practitioners

Christina Yiallouridou,[1] Jennifer H Acton ,[1] Sanjiv Banerjee,[2] Heather Waterman,[3] Ashley Wood [1]

To cite: Yiallouridou C, Acton JH, Banerjee S, *et al*. Pain related to intravitreal injections for age-related macular degeneration: a qualitative study of the perspectives of patients and practitioners. *BMJ Open* 2023;**13**:e069625. doi:10.1136/bmjopen-2022-069625

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-069625).

Received 27 October 2022
Accepted 01 August 2023

[1]School of Optometry and Vision Sciences, Cardiff University, Cardiff, UK
[2]Ophthalmology, Cardiff and Vale University Health Board, Cardiff, UK
[3]Healthcare Sciences, Cardiff University, Cardiff, UK

Correspondence to
Dr Ashley Wood;
WoodA2@Cardiff.ac.uk

ABSTRACT

Objectives Ocular pain is a commonly reported finding in the intravitreal injection procedure, but post-injection experiences and patient adherence to treatment remain underexplored. We therefore aimed to identify key variations in the intravitreal injection procedure that may influence pain, and to gain insights into the post-injection experience and treatment adherence from the perspective of patients and practitioners.

Design Qualitative semistructured interview study using reflexive thematic analysis of transcripts.

Setting Hospital Eye Clinic in Wales, UK. Interviews were conducted between May and September 2019.

Participants Purposive sample of patients aged ≥50 years with neovascular age-related macular degeneration and no other retinal pathology who had received at least six intravitreal injections, and practitioners including ophthalmologists, registered nurses and optometrists who performed intravitreal injections at the research site.

Results Data saturation was reached with 21 interviews: 14 patients and 7 practitioners. Three main themes were identified from the analysis: fear of losing eyesight and treatment anxiety influence patient adherence to treatment, variability in pain experience during treatment, and post-injection experience and impact on patient recovery. To reassure patients feeling apprehensive about the injections, practitioners promoted safety and trust, and used techniques to manage anxiety. Key variations that may influence pain identified were application of antiseptic or anaesthetic, injecting methods and communication. During injection, patients reported a dull-aching and sharp pain, contrary to practitioners' perspective of feeling a 'pressure'. Patients described prolonged soreness and irritation of up to 36 hours post-injection affecting their sleep and recovery.

Conclusion Establishing rapport supported patients to recognise the necessity of ongoing treatment to prevent sight loss; however, inadequate pain management led to undesirable outcomes. Practitioners should use pain assessment tools during and immediately after injection and provide ongoing consistent information to help patients manage pain at home.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The qualitative approach allowed us to gather detailed descriptions of the pre-injection, peri-injection and post-injection experience of patients and their adherence to treatment.
⇒ The study explored the perspectives of patients and practitioners to gain a comprehensive understanding of the patient experience; triangulation facilitates credibility and validity of our findings.
⇒ A limitation of this study was that the participants were recruited from one eye clinic; patients' experiences may vary across hospitals, particularly where protocols for intravitreal injection differ.
⇒ The study methodology limits transferability; however, we obtained data saturation through in-depth interviews and thoroughly described the research context.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of vision impairment worldwide accounting for 8.7% of cases,[1] with the neovascular subtype resulting in the most severe and rapid vision loss.[2] AMD-associated vision loss can affect activities of daily living, including reading and driving, increasing the prevalence of isolation, loneliness and depression impacting on quality of life and economic independence.[3] While there is no cure for AMD, regular intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents are the most effective treatment for impeding disease progression associated with neovascular AMD and for preserving eyesight.[4] Despite the well-established clinical efficacy and safety of anti-VEGF injections, patients can experience ocular pain during treatment,[5] which can affect patient adherence, potentially hastening vision loss.[6]

Patients can currently be treated using anti-VEGF agents ranibizumab,

aflibercept, brolucizumab or faricimab, while bevacizumab is unlicensed in the UK and pegaptanib no longer recommended. Treatment regimens typically consist of 'loading phase' with three injections at monthly intervals, then a follow-up and retreatment regimen. Typically, 'pro re nata' involving fixed interval review with treatment given if neovascular activity is detected, or 'treat and extend' where treatment is given at each review, but the interval extended if neovascular activity is not detected.[7] These regimens continue indefinitely or until a clinical endpoint is reached.

Patients are estimated to receive 14 injections on average in the first 2 years of treatment with ranibizumab,[8] and could experience pain during any of the injection procedures. Despite well-developed regimens that reduce the burden of frequent appointments[9] and improve visual outcomes,[10] patients can still expect many injections.[11] Since pain is a subjective experience, self-reporting by patients is considered the most valid measure.[12] Several studies have assessed pain using numerical or Visual Analogue Scales to investigate the type of anaesthetic,[13 14] the InVitria assisting device,[15] injection site[16] or needle size.[17 18] Tailor *et al*[19] used a non-standardised questionnaire that divided the injection procedure into 10 discreet procedural steps each scored using a Visual Analogue Scale reporting varying levels of patient discomfort for the placement of speculums, and the application and removal of drapes. However, the wide variation in pain scores reported suggests that the appropriateness of numerical pain scales to describe the individual experience is equivocal.

Previous literature investigating patients' experience of anti-VEGF injections has evaluated anxiety,[20] quality of life[21] and adherence to treatment.[22] One such study used narrative interviews, although pain was not the principal focus.[23] However, there is a need to explore patient–practitioner communication and their shared understanding of benefits of treatment and information provided, and to assess how practitioner behaviour can influence patient adherence and experience of treatment.

The importance of patient–practitioner interaction has been highlighted in qualitative studies of the experience of patients with neovascular AMD[5 23–26]; however, there is a paucity of literature describing qualitative perspectives in the assessment of pain and anxiety related to anti-VEGF injections that incorporate a practitioner perspective. This study examined patients' experiences of injections and combined them with the practitioners' views from a qualitative perspective.

The objectives were: (1) to identify key variations in treatment procedures that may influence pain, and (2) to gain insights into the post-injection experience and treatment adherence.

METHODS

Study design

Using a qualitative design, one-on-one semistructured interviews were conducted with patients and practitioners to explore and understand the meaning of individual experiences.[27] The research team comprised a multidisciplinary group with expertise in clinical ophthalmology, pharmacology and population health to provide a broad spectrum of perspectives on the themes generated.

Participant recruitment and sampling

Patients and practitioners were recruited from a hospital eye clinic in Wales, UK.[28] The provisional sample size ranged between 10–20 patients and 8–10 healthcare practitioners, informed by models of qualitative research.[29] Participants were purposively selected[30] to include a representative range of patients with respect to age, sex, number of injections and, where possible, ethnicity. An opportunity sample of practitioners was based on the total number of injectors at the site. Data saturation relied on the researcher's interpretation of addressing the research aims and reaching consensus on the data collected.[31] Data saturation was reached when the researcher deemed that there were three consecutive interviews without additional material arising.[32]

Inclusion and exclusion criteria

Patients were eligible if they were aged 50 years and above, had a diagnosis of neovascular AMD, received at least six intravitreal anti-VEGF injections and were able to provide informed consent. Exclusion criteria for patients included retinal pathology other than neovascular AMD, suffering from very poor hearing or unable to communicate in English or Welsh. Practitioners eligible for participation consisted of those who were ophthalmologists or registered nurses and optometrists and performed intravitreal injections during the course of the study. Practitioners who were unable to communicate in English or Welsh were excluded from the study.

Topic guides and data collection

The topic guides (online supplemental files 1 and 2) were developed from themes that were identified from reviewing the literature on patients' experiences of intravitreal injections. Interviews consisted of open-ended questions allowing participants to express personal experiences and views on the topics discussed.[28] A flexible approach permitted the researcher to adapt to the responses using probes and member checking to gain more information of the topic under investigation and to ensure participants' meanings were understood as intended.[28] In this context, interview questions evolved from the planned topic guide. During the interview, participants were asked to consider their experience of all the injections they have received since diagnosis.

Interviews were conducted between May and September 2019. The researcher explained the aims, expectations and nature of the study before taking consent, and

reassured participants of the confidentiality of their data. Patient interviews occurred either in the participant's own home or in a private meeting room at Cardiff University, according to the individuals' preference. Practitioner interviews were conducted at their workplace office. Interviews were audio recorded using an Olympus VN-541PC voice recorder and analysed by the first author (CY). The researcher had no prior experience with qualitative research interviews and has attended training workshops and received guidance from a supervisor with broad experience in interviewing and qualitative research.

Data processing and analysis

Interview data were transcribed verbatim, pseudonymised and thematically analysed using a reflexive (inductive) approach,[31 33] with the support of NVivo (V.12, QSR International) data analysis software. The six-phase procedure suggested by Braun and Clarke[33] included familiarising with the data, initial coding and labelling of data, searching for themes, reviewing themes, defining and naming themes, and producing the report. Thematic analysis allows perspectives of different participant groups and similarities and differences to be highlighted. Data source triangulation was used to strengthen our findings by collecting data from patients and practitioners.[34] Thematic analysis is not bound to a specific epistemological position[33] and in this study is regarded as a method in its own right to address the research aims.

A preliminary thematic scheme was initially developed and reviewed by the first author (CY). Using a collaborative approach,[31] transcripts (four patient cases, three practitioner cases) were randomly selected and independently coded by the two authors (JHA and AW) to engage in a richer, more nuanced reading of the data, improving rigour of our analysis. The data analysis was primarily conducted by the first author (CY) who had no previous experience in working with intravitreal injections. A journal was also kept to document thoughts and decisions made throughout the study to facilitate reflexivity.[28] Producing the report, themes were reviewed and modified as required to support the interpretation of selected extracts related to the research aims. This study adheres to the Standards for Reporting Qualitative Research guidelines[35] (online supplemental file 3).

Patient and public involvement

The research question and study design were informed by patient views elicited from feedback of a local patient group with macular disease. A summary of study results was sent to all participants who requested it.

RESULTS

Characteristics of study participants

Participant characteristics are presented in table 1. Patients and practitioners had a median age of 82 (range 70–95) and 37 (range 28–59) years, and had a median number of 18 (range 6–50) injections and 3 (range 1–11) years of injection experience, respectively. All participants were English speaking. Patient and practitioner interviews ranged from 14 to 45 min and 10 to 35 min, respectively. Participants are identified as PA for patients and HP for healthcare practitioners, followed by an identification number.

Table 1 Patient and practitioner characteristics

Participants	Characteristic	Value
Patients	Age, median (range), years	82.5 (70–95)
	Female sex, no (%)	9 (64)
	Number of injections, median (range)	20.5 (6–50)
	Place of primary residence, no (%)	
	Lives alone	6 (43)
	Lives with family	8 (57)
Practitioners	Age, median (range), years	37 (28–59)
	Female sex, no (%)	6 (86)
	Qualification, median (range), years	9 (6–19)
	Injection experience, median (range), years	3 (1–11)
	Occupation, no (%)	
	Nurse	4 (57)
	Ophthalmologist	2 (29)
	Optometrist	1 (14)

Qualitative results

Data saturation was reached with 21 interviews: 14 patients and 7 practitioners. Thematic analysis revealed three main themes: (1) fear of losing eyesight and treatment anxiety influence patient adherence to treatment; (2) variability in pain experience during treatment; and (3) post-injection experience and impact on patient recovery. Supporting quotations are presented in tables 2–4, respectively, and table 5 compares patients' and practitioners' responses within the themes.

During analysis, we were able to identify the following key variations that may influence pain: first, the application of antiseptic and/or anaesthetic. Patients felt different amounts of antiseptic or anaesthetic agents led to differences in the associated burning sensation and affected the overall level of pain experienced. Second, the methods used in carrying out the injection (eg, injection site) were felt to affect the outcome related to pain. Third, the way in which the practitioner communicated was considered important, in the context of providing reassurance or employing distraction techniques.

Theme 1: fear of losing eyesight and treatment anxiety influence patient adherence to treatment

Patients highlight fear of sight loss as outweighing the burden of chronic treatment as drivers of adherence, but considerable anxiety experienced attributed to uncertainty surrounding each injection (see table 2 for illustrative quotations). In the context of the first subtheme, anxiety and uncertainty surrounding each injection, the

Table 2 Fear of losing eyesight and treatment anxiety influence patient adherence to treatment

Themes/subthemes	Illustrative quotations of patients (PA) and healthcare practitioners (HP)
Anxiety and uncertainty surrounding each injection	
Fear of the 'unknown' and the feeling of suspicion	'It's always the unknown which is more scary.' (HP6)
	'So, I was a bit concerned when I went up and had the thought of having an injection in your eye.' (PA01)
	'But you know what's coming when she says don't move…And you're afraid that you'll move.' (PA06)
	'Because you know, just getting anxious, lying down there.' (PA11)
	'Some people just don't like having the injection full-stop. They just get so anxious!' (HP2)
	'Nobody likes to come and have injection in their eyes. It's not a nice procedure anyway. Even the thought of it.' (HP5)
Coping mechanisms to manage apprehension	'I ask them to take a deep breath. Most of them they say it's very nice because they concentrate on breathing and they don't feel it.' (HP5)
	'The nurse always holds your hand. I feel more relaxed.' (PA11)
	'I try to tell them to focus on their breathing and to wiggle their toes basically give them something to focus on. It should have like a tv screen of nice, relaxing music. For people to start meditating, focusing on their breathing, and just relaxing.' (HP4)
	'Um you just got to be very patient with them and just try and reassure them.' (HP3)
	'I like the opportunity of communicating. It eases the nervous tension.' (PA05)
Attitudes and emotions related to chronic therapy as drivers for treatment adherence	
Feeling lucky and grateful	'I'm very grateful to the NHS because the injections I know are very expensive.' (PA14)
	'That's what it is you know. If they're going to do something to see if they can help me. Well, you know. Carry on!' (PA04)
	'I'll do anything to keep my sight.' (PA13)
Feeling worried to stop receiving treatment	'I always have it every 8 weeks… One time I went for 11 weeks and that really worried me because I thought, oh my goodness what's going to happen to my eye?' (PA03)
	'…occasionally it's been a bit longer than six weeks which I'm not very happy about. Because I don't think it should be longer than six weeks.' (PA02)
	'…one consultant even suggested um discharging me from the clinic. I was a little worried about that…I wouldn't like to be discharged and then have to rely on my own judgment.' (PA14)
In adherence to treatment	'Whatever the treatment is, you just have to have it. Not the most pleasant.' (PA12)
	'And of course, now I see the results that they did. My eyesight is improving. I don't think I'd continue with it if I couldn't see an improvement.' (PA07)
	'It is over so quickly, and I don't think I would ever turn it down. I wouldn't say I can't have it done, you know…' (PA06)
	'I find it marvellous really. I'm pleased with the way it's gone, and I can see my daughter and watch the news more.' (PA01)

NHS, National Health Service.

fear and apprehension are described with respect to the steps of a treatment episode. The second subtheme, attitudes and emotions related to chronic therapy as drivers for treatment adherence, encapsulates the fear arising from the entire course of treatment.

Anxiety and uncertainty surrounding each injection

The thought of having a needle entering the eye, and particularly living with the uncertainty of what the procedure might entail was most frightening for the majority of patients. This may be of an unexpected 'unknown' complication occurring or informed by a previous adverse experience:

> When you see them filling the injection, I'm thinking, oh don't look at the needle. (PA03)

Remembering a painful past experience, patients worried about injury to their eye:

> That was the worst experience… She grabbed the needle and then she couldn't get the needle out. So, it did hurt quite a bit. (PA07)

In comparison, the practitioners perceived patients to be experiencing feelings of apprehension such as fear, anxiety and suspicion prior to and during the injection procedure. The practitioners used their observations of patients' reactions to help the patients to develop coping mechanisms to manage treatment-related anxiety. Examples included rapport-building, reassurance and distraction techniques, such as handholding or asking them to focus on their breathing or wiggling of their toes (see table 2).

Some patients were given a warning or indication of impending injection (eg, 'don't move' (PA06)); distraction techniques were commonly reported by patients and practitioners. It was equivocal if warning or distraction achieved the best outcome.

Table 3 Variability in pain experience during treatment

Themes/subthemes	Illustrative quotations of patients (PA) and healthcare practitioners (HP)
Preparation steps	
Instillation of anaesthetic eye drops	'When they put the drops on, the second one I think it is, makes it burn a little bit.' (PA04)
Application of chlorhexidine/ povidone-iodine	'It stings for a second but then when they start putting the other injections…you don't know it's there.' (PA03)
	'I am allergic to the iodine. It burnt my eyes. I couldn't see and it was painful…It took a long time to wear off.' (PA12)
	'The iodine makes the surface of the eye very fragile.' (HP6)
Placement of eyelid speculum	'It wasn't painful it was just part of the routine of giving enough space to put the needle in.' (PA13)
	'…some nurses have more difficulty than others getting it in correctly, so that you can't blink. But they eventually get it right and that's fine.' (PA14)
Placement of surgical drape	'The thing that goes over your face [the drape] that's not very nice… I was scared when I went the first couple of times, but now I got used to it.' (PA09)
Intravitreal injection: expecting versus experiencing	
Pressure	'But it's all of a sudden having a pressure on the eye as the needle tries to break through the surface.' (PA08)
Stress and tension	'And because it hurts, I tend to hold my breath and tense up.' (PA07)
Pain	'But sometimes I just feel like the injection you get when you're having your tooth out. Very mild pain.' (PA05)
	'The pain is only instant… As soon as they pull the needle out, the pain is gone.' (PA08)
	'And to tell you the truth, it's over in a second.' (PA03)
	'I don't think pain is static. I think pain threshold varies depending on what patient's like on that day.' (HP4)
	'I didn't have enough anaesthetic. It was quite sharp.' (PA12)
	'It is just like a pinprick only a bit harder.' (PA10)
Injection technique	'Have you hold the bevel horizontally, obviously it will hurt cause you're cutting like two or three fibres. As if you hold it parallel to the sclera fibres, then you squeeze it between two sclera fibres without cutting any… That's something that you learn from your knowledge of anatomy, also from experience.' (HP6)
	'The injections vary. It's like anything that involves a technique. Some nurses and doctors have a better technique than others.' (PA14)
'Better than anticipated'	'And the first one, I must say, I came out and said, well, that's certainly wasn't as bad as it sounded.' (PA06)
	'It's bearable. I'm sure there are much worse things than having this done…It's painful, but over very quickly.' (PA06)
Impact of quality of care delivery on patient experience	
Observation and reflective practice	'One patient would come and say, oh I felt that…Of course you would reflect…What could have I done better? It's constantly improving your practice based on what the patient has told you.' (HP7)
	'If patients have blepharitis…I put an extra bit of iodine, rub the iodine closely around the eyelids and the eyelashes.' (HP6)
	'I was doing two eyes, so I did the right eye and if that was a little bit painful, I would probably put a little bit more anaesthetic in the other eye just to see if that helps, you know, to try and combat that.' (HP2)
	'What I do is when they had a drop of iodine in after the anaesthetic, I ask if it stings. If it stings, then maybe they need more anaesthetic.' (HP3)
Respectful and acting professionally	'We try to be very professional. We will not show that we feel like that [fatigue].' (HP5)
	'You can feel that towards the end you might be tired…My principle is how I treat my first patient that would be the same quality that I treat my last patient.' (HP7)
Individualised patient care	'…the InVitria [assisting injection device] might not be a good idea, so I put a drape for anxious patients. Because you need patients' cooperation when you want to put the InVitria.' (HP6)
	'But if my patients are uncomfortable, sometimes, they can't move from the wheelchair to the chair. We still do our best to give them injection while they are in the wheelchair which is a really difficult situation.' (HP5)
	'We adjust to the patient. Let's say we have a little old lady who cannot stretch herself at the chair, we offer to give her the pillow.' (HP7)
Making decision and clinical judgement	'Make sure that you're injecting in the area that there's no vessels, because you don't want to cause any bleeding afterwards.' (HP2)
Lack of assessment tools to evaluate pain	'We don't use any tools, but we provide psychological support. For example, we talk to them…How was your weekend? How was your holiday?' (HP5)
	'…we don't have a way of measuring pain threshold.' (HP4)

Attitudes and emotions related to chronic therapy as drivers for treatment adherence

Practitioners' interaction with patients to explain how they could benefit from injections was an important factor in adherence. Understanding treatment benefits for preserving eyesight influenced patients' intention to accept the treatment plan:

> I would never discontinue the treatments because that's what enables me to still read and drive. (PA14)

Some patients also expressed concerns about disease progression when their appointment was rescheduled to a later date. Despite initial concerns, patients expressed being thankful and grateful for the treatment, generally

Table 4 Post-injection experience and impact on patient recovery

Themes/subthemes	Illustrative quotations of patients (PA) and healthcare practitioners (HP)
Post-injection experience and impact on patient recovery	'Floaters, sometimes spots in the eye that sort of flick around a little bit. But normally after a day or two it wears off… It's like having a fly in your eye…' (PA08)
	'And sometimes you have a lot of floaters. It can leave you with a little sort of floating disks, but they are temporary, they go.' (PA14)
	'I get a taxi to come home because my vision in the eye that does have the injection is a bit blurry when I go out to the hospital.' (PA04)
	'I've had occasions when it waters a lot and occasions when it feels you got sand in your eye.' (PA03)
	'…there's a big black blob…it's like a black mess.' (PA06)
	'Sometimes, you got a feeling of soreness in the eye, a little pain.' (PA05)
	'The iodine dries the eye out, so they get discomfort that night and the next day.' (HP1)
	'Very often when they come out of the injection, they start blinking or they rub their eyes and this will create a scratch, corneal abrasion. This is very painful once the anaesthetic goes away…' (HP6)
	'I have had a headache sometimes. I don't suffer with headaches, never have. But um, I sort of have an ache just by there [demonstrates on side of eye]. I do feel very tired after I've had it done.' (PA09)
	'When the numbness wears off, it then starts to feel a bit sore so often.' (PA11)
	'Now and then you can have just a slight bleed because…I tend to move my head and I might scratch the eyeball. And that needs more treatment to an extent.' (PA05)
	'The aftereffects of the injection I think are worse than the injection itself… Little pain, a little discomfort, a little dryness…It's only for maybe 24–36 hours and then it's fine.' (PA14)
Home remedies for ocular pain	'I do not think they need chloramphenicol. I think they just need lubrication…That would improve quite a lot of people's discomfort afterwards.' (HP1)
	'If they feel that they would have any discomfort, I will always advise them to take some paracetamol if they wanted to.' (HP3)
	'After the injection sometimes, I take a couple of paracetamol.' (PA05)
	'When you get home take couple of paracetamol or whatever painkiller you have, couple of hours of sleep and you will be fine…' (HP5)
Instructions and provision of patient information leaflets	'And give warning to the patient that if their pain is increased, floaters, flashes of light reduce the vision.' (HP4)
	'Tell them about the antibiotics they need to take. So, we give antibiotics [chloramphenicol] for four days after the injection. We give them some leaflets if they need to have, emergency contact numbers and then if everything is okay then there's no problem, the patient will go home.' (HP2)
	'They give these eyedrops [chloramphenicol] which you have to use four times a day for four days. They were of help.' (PA05)
	'Sometimes the pressure can go up after the injection and that can give pain… In future, tell them to take Diamox [acetazolamide], a pressure loading tablet before you inject.' (HP6)
	'Next day, you get floaty things and think, I hope that's all right. But then you look at the leaflets and yes, that can happen.' (PA06)
	'We will give the antibiotic to take home and the instruction on how they will have it, and a proper leaflet, in case there is any problem when they go home…' (HP7)
	'Came home and complied with their instructions…They gave me the antibiotic and used it four times a day for four days.' (PA13)

perceiving fear of loss of eyesight as more important than their apprehension about the treatment:

> It's a very small thing to pay to keep your sight. I think that is excellent and we are very lucky to have it. (PA10)

Theme 2: variability in pain experience during treatment

Variability in the level of pain was experienced during treatment. In the first subtheme, patients and practitioners recognised preparatory procedural steps, and the second subtheme, 'intravitreal injection: expecting versus experiencing', highlights both expectation and experience of pain during the injection. While the final subtheme, impact of quality of care delivery on patient experience, identified the value of individualised care to improve patient experience (see table 3 for illustrative quotations), apparent dissonance existed between patient experience and practitioners' expectation of pain.

The variability in pain experienced during intravitreal injections arises from a range of influential factors, including both physical and psychological elements. Inconsistent application of anaesthetic and antiseptic agents, variations in injection techniques and individual pain perceptions all contribute to this wide-ranging variability. Patients describe a diverse spectrum of pain experiences, ranging from dull-aching to sharp sensations, with some attributing the intensity to a perceived inadequacy of anaesthesia. Furthermore, psychological factors such as anxiety, fear and expectations play a key role in shaping the pain experience during the procedure.

Table 5 Comparison of patients' and practitioners' perspectives on the treatment experience

Main theme	Subtheme(s)	Illustrative quotations		Comment
		Patients (PA)	Practitioners (HP)	
Fear of losing eyesight and apprehension on patient adherence to treatment	Fear of the 'unknown' and the feeling of suspicion	'I mean the fact that I would just have to have a needle in my eyeball is not very good.' (PA02)	'Normally patient says it's the thought of it you know… they just feel lining something in their eye. They are startle.' (HP4)	Agreement
	Coping mechanisms to manage apprehension	'I'm now going to give you the injection [they say] …they prepare you for it.' (PA14) 'They always do it. When you're in a chair, you don't know where to put your hands really. And she would always hold your hand.' (PA09)	'I explain step by step, so they're involved. Most patients, I realise, they like that.' (HP5) 'If there is someone who is particularly anxious the healthcare assistant would always make sure they hold their hand, so they got some sort of comfort there.' (HP1)	Agreement
	In adherence to treatment	'So relieved to find you could have some treatment that you didn't really mind. It was better than nothing.' (PA12) 'Well one of my consultants. And he was very reassuring. And I put my confidence and trust in him.' (PA05)	'…talking to the patients in a nice way, in a gentle way, sometimes you can convince them of the benefits of an injection.' (HP6)	Agreement
Variability of pain perception during injection	Intravitreal injection: expecting versus experiencing	'…there's a sting and a pressure. And that's the same…that's the only way they can get it in you know.' (PA06) '…they say, it's a common practice, you don't experience any pain, but you do. It's not pleasant.' (PA07)	'There is a lot of anaesthetic used… you should not feel anything from that side of things… What they should really feel is a pressure…' (HP1) '…you can reassure them that this is not going to be painful.' (HP6)	Dissonance
	Impact of quality of care delivery on patient experience	'She said, I like to wait.' (PA06)	'The time is not a bad thing because you need time for the anaesthetic to work better and for your iodine to clean the eye better. Sometimes working too quickly is not a good idea.' (HP6)	Agreement
		'And she always gets hold of your hand just to reassure you, so she can feel the tension that's going in there.' (PA08) '…she will lift the corner up [of the drape] and just so I can get fresh air, which is fine.' (PA08)	'If there is someone who is particularly anxious the HCA [healthcare assistant] holds their hand, so there that they have got some sort of comfort there.' (HP1) 'If they've got breathing problems…I would probably get my colleague to sort of hold up the corner [of the drape]…so their face is not so covered.' (HP2)	Agreement
Post-injection experience and impact on patient recovery	Instructions and provision of patient information leaflets	'And before I left the hospital I went to my consultant and told him and he said, don't worry. Blurriness will clear very quickly. And it did.' (PA05) 'And I mustn't rub it, you know.' (PA14) 'It's antibiotics. And you have to take them 4 times a day, 16 altogether. And they say you can carry on. Sometimes I do it for 5 days.' (PA03)	'It gives a bit of a blur initially…you have to explain these things to them. If they're not being informed about it, they ring because they're worried about it.' (HP6) 'Give them careful instructions not to rub the eye.' (HP6) 'And if your eye is dry or gritty, you can use more of that [Chloramphenicol], it won't harm. It just eases the eye, like you know, the grittiness and the dryness of the eye.' (HP5)	Agreement
	Home remedies for ocular pain	'They just say to take paracetamol if you do [feel pain].' (PA06) 'I get a like a compress with hot water to hold of my eye.' (PA14)	'If they felt that they would have any discomfort, I would always advise them to take some paracetamol if they wanted to.' (HP3) 'I think most of them will kind of go to bed with a cold compress on their eye afterwards. That is what they generally report.' (HP1)	Agreement

Pain experienced during the preparation steps

The preparatory steps are essential for ensuring the safety and comfort of the intravitreal injection procedure. To minimise pain, topical oxybuprocaine 0.4% was applied as an anaesthetic. Antiseptic agents, such as povidone-iodine or chlorhexidine, were carefully used to sterilise the surrounding area. A surgical drape was then positioned to maintain sterility, and an eyelid speculum was inserted for improved access.

Practitioners agreed on the importance of adhering to sterile conditions for injecting. A stinging sensation during application of the anaesthetic eye drops (topical oxybuprocaine 0.4%) and povidone-iodine or chlorhexidine was commonly reported. Both patients and practitioners commented on the apparent inconsistency in the procedure for applying anaesthetic and antiseptic agents (see table 3). This inconsistency can be attributed to variations in practitioners' techniques, the frequency of administration, individual sensitivity to these agents and the time intervals between treatments. These factors collectively contribute to the observed variability and potential inconsistencies in their application. Patients also reported different opinions on the drape application:

> I find it [the drape] a little bit, um awkward… I'll do say, do you mind if I don't use it because I hate breathing warm air. I feel uncomfortable with that on. (PA08)

> Well, I'm glad when that's [the draping] done. Because you can see the needle otherwise… (PA11)

Intravitreal injection: expecting versus experiencing

Ranibizumab or aflibercept was commonly used anti-VEGFs in this clinic. Most patients experienced a stinging sensation or reported a 'bump' felt on the eye upon needle entry, or 'breaking through the surface'. A key variation was identified in the visit experience attributed to perceived methods used in carrying out the injection which was felt to affect the outcome related to pain (see examples of different methods in table 3, for example, needle position). The pain experience varied across individuals some described it as dull aching, mild, like a 'pinprick' or 'when you're having your tooth out', while others experienced a sharp pain because of perceived lack of anaesthesia. The needle insertion was described as painful, but most patients perceived the injections as instant and bearable.

One patient used stronger language to describe the experience:

> You then wait for the torture, I call it… The injection. It's a bad experience. When they push the needle into your eye, it's like a dull aching pain… (PA07)

On the other hand, practitioners reported that it is unusual to encounter patients who experience pain. See the Comparison of patients' and practitioners' perspectives on the treatment experience section for further examples of the dissonance between patients' and practitioners' perceptions of the patient experience.

The practitioner further explained that a skilled injection technique required 'knowledge of anatomy' and 'experience' to lessen a painful injection, consistent with patients' perception of the technical ability of the individual performing the injection:

> I hold the bevel parallel to what I know the anatomical alignment of the sclera fibres. Then when you go in, you don't really cut any of these fibres. That's when the pain is felt less. (HP6)

Impact of quality of care delivery on patient experience

Practitioners explained that their level of expertise relied on their ability to make clinical judgements, and upon continual learning and evaluation of performance. When patients reported pain, one nurse practitioner participant described that this led them to reflect on their practice.

Staff made individualised adjustments depending on the specific needs of the patient, which impacted on the overall comfort of the patient, with the potential for less anxiety and reduced perception of pain. Strategies were adapted, such as applying more anaesthetic or waiting longer than normal for the anaesthetic to take effect:

> If you give a bit of more time for the anaesthetic to settle is a much better experience for the patient… That patient might be somebody whom you need to wait for a little bit more. (HP7)

The injection procedure was demanding, but the practitioners acknowledged that their interactions affected patients' experiences:

> Talk to the patient… You want to make them feel as they can trust you and that's a really important part to get that sort of therapeutic relationship going… Patients will know you. They will know how you work, and they will know exactly what to expect… (HP2)

Theme 3: post-injection experience and impact on patient recovery

The experience of patients following their injections and recovery was discussed with painful or discomforting side-effects highlighted as negatively impacting patient experience and recovery. Patients experienced blurred vision, 'floaters', watery eyes or grittiness (see table 4). Many patients also reported eye pain, eye irritation or itchiness following their injection, and some associated their experiences with headaches and the anaesthetic wearing off, also leading to trouble resting or sleeping:

> Very often I'm getting very gritty and sore… I can't sleep, honestly because of the irritation is there all the time… It's very itchy. (PA08)

Soreness and irritation were the most common experiences following an injection, usually lasting between 24 and 36 hours. Practitioners explained that povidone-iodine may cause the eye to dry out after the injection and

blinking or rubbing the injected eye may further cause corneal abrasion which can contribute to pain.

Home remedies for ocular pain

Pain resulting in sleep disturbance had negatively impacted patients' recovery. To manage post-injection experience, one patient deliberately scheduled the appointment early in the day to avoid having problems sleeping at night and reported applying a hot compress after the injection:

> If you have an injection first thing in the morning, if there is any discomfort, the worst is over by the time you go to bed… If it's a late injection and my eye is very sore, then I might have a very restless night… I get a like a compress with hot water on my eye. (PA14)

Practitioners generally advised patients to take their usual pain relief medication including paracetamol or ibuprofen to manage any pain at home.

Instructions and provision of patient information leaflets

Both patients and practitioners highlighted the importance of recognising aftereffects, their management and how this can improve patient experience and recovery (see tables 4 and 5 for illustrative quotations), this included provision of instructions and patient information.

Consistent with clinical protocol, clear instructions and provision of information leaflets educated patients on their antibiotic prescription, common side-effects and potential complications (see table 4). All patients read the leaflets and were instructed to use chloramphenicol antibiotic eye drops four times a day for 4 days. The leaflets addressed concerns regarding post-injection eye appearance, vision changes, and emphasised prompt contact with the urgent eye clinic for any specific symptoms or concerns. This was reported as reassuring to patients. Practitioner communication in the context of advising and providing reassurance was identified as a key variation impacting on the patient experience.

Comparison of patients' and practitioners' perspectives on the treatment experience

Practitioners unanimously acknowledged the fear and apprehension experienced by patients before intravitreal injections through observation, addressing concerns and creating a supportive environment. Some practitioners asserted that patients primarily feel pressure rather than pain during the procedure, focusing on the use of anaesthetics to minimise discomfort. They reassured patients that any sensations are temporary and manageable, aiming to alleviate pain-related concerns. However, not all practitioners shared this viewpoint. Some recognised patients' reports of discomfort or pain, acknowledging the individual variability in pain perception. They prioritised empathy and reassurance, implementing additional measures to ensure patient comfort. Despite these differing opinions, all practitioners agreed on the importance of high-quality care addressing patient fears, offering clear explanations and highlighting patient education. This includes educating patients about home remedies like cold compresses and over-the-counter pain relievers to manage any post-injection discomfort or pain, and emphasising adherence to treatment. Table 5 presents exemplar quotes that highlight the overall comparisons discussed.

DISCUSSION

Building on previous research[13 14 19] that focused on quantitatively assessing pain during anti-VEGF treatment, this study examined patients' and practitioners' perspectives using an in-depth qualitative approach to gain insight into patient experience and treatment adherence. These findings contribute to an increased understanding of the patient experience by indicating that post-injection ocular pain is more common than previously recognised with soreness and irritation experienced up to 36 hours following most anti-VEGF injections, while also affirming experiences reported in similar cohorts.[23] The analysis showed the value of patient–practitioner interactions to facilitate understanding of treatment expectations and individual needs, and highlighted where practitioners can assess and best address advice to patients for controlling pain before and immediately after injection.

Pain is commonly induced by ocular surface irritation, vitreous inflammation or an increase in intraocular pressure (IOP).[11] Most patients reported side-effects including grittiness, soreness and irritation 4–6 hours after treatment, with the latter likely to be associated with the return of full corneal sensitivity 40 min after application of anaesthesia, or because of the irritant properties of iodine.[36] Long-lasting ocular pain between 24 and 36 hours was found in the present study, but has not been previously reported in studies of patient experience.[5 23] However, headache reported in this study has been previously associated with an elevated post-injection IOP[37] and found in individuals who experienced episodic migraines following anti-VEGF treatment.[38] Practitioners referred to reviewing patients' medical records to determine history of allergies, ocular infections and IOP to treat patients accordingly.

Our findings align with previous literature in that providing clear instructions and acknowledging patient concerns or expectations build rapport and can contribute to a positive patient experience.[39] Provision of information leaflets after treatment helped patients in the study to recognise common side-effects, providing a form of reassurance. Additionally, instructing patients on their prescription antibiotics or not to rub their eye after the injection can help reduce the risk of itching and pain, previously reported to influence patient engagement with treatment.[5] However, the chronicity of AMD and the routine nature of the anti-VEGF injections could lead patients to perceive pain as less salient, influenced by previous experiences and the variable intrainjection experiences reported in this study. Practitioners should

consider routinely warning patients of potential pain and advice on home remedies for ocular pain relief, such as local ice compress and analgesic use.[40] Ice, for instance, had shown effectiveness as a local anaesthetic during injection[41] and cooling-based anaesthesia.[42]

Repeated injections have been linked to morphological changes to the sclera and believed to contribute to greater difficulty with needle insertion.[43] This study could not substantiate these observations; nevertheless, patients revealed a degree of pain during injection consistent with previous findings reporting a 'little prick' and sharp sensation.[23] Our analysis reports dissonance between patients' expectations and their actual experiences during injection. Some patients reported a pressure, but others experienced a dull-aching, sharp or just a mild pain, different to practitioners' views on a feeling of pressure. Practitioners typically use the term 'pressure' to reassure patients; however, mutual trust and providing realistic expectations are important aspects of treatment.[6] Practitioners reported the importance of technical competency and continuing professional development. This is consistent with professional guidelines,[11] indicating that practitioners should periodically review and evaluate their performance.[44] Not all practitioners acknowledged the proportion of patients experiencing pain and this highlights the importance of implementing patient feedback.

Moreover, despite the extensive literature comparing the effect of different anaesthetic techniques to address pain during an intravitreal anti-VEGF injection,[13 14] no method of anaesthesia has been shown to eliminate pain completely; it is common for patients to experience mild pain during injection.[45] A 0.4% solution of oxybuprocaine used in the clinic under study delivers a maximum anaesthetic effect after 5 min when administered at 90-second intervals and lasts for 15–20 min.[46] Our findings support allowing enough time to reach adequate anaesthesia; however, alternative methods may be investigated to meet patient needs, such as subconjunctival injection and anaesthetic gel.[13]

Increased pretreatment anxiety has been significantly related to greater perceived pain during injection.[47] Anticipatory anxiety can lead to oversensitivity[48] and muscle tension around the eyes and face.[49] In this study, apprehension was attributed to being able to see the surgical needle and patients' fear of an eye injury leading to muscle tension and 'jumping' reactions. These have occasionally affected the practitioner injecting, altering needle position and causing an abrasion to the eye. In emotion theory, startle and pain are described as innate automatic reflexes or reactions in response to existing stimuli.[50] Patients could learn using deep breathing exercises to initiate muscle relaxation,[51] helping themselves manage apprehension more effectively.

Non-adherence has previously been linked to fear of the injection and disbelief regarding its benefits.[23] Our study supports that establishing and maintaining a therapeutic relationship contributes to patients' confidence and engagement with their treatment course.[52] Patients' motives for continuing treatment were related to their understanding of the severity of the consequences of untreated AMD and the treatment benefits, giving them the ability to carry out daily living activities.

Strengths and limitations

A key strength is the combined data from both patients and practitioners. Purposive sampling can be prone to researcher bias; however, to minimise this, judgements were based on the eligibility criteria of the sample. Individual interviews were conducted in a private setting assuring participants of the confidentiality and anonymity of their data to reduce social desirability response biases. In addition, interviews were conducted by an inexperienced interviewer and could have impacted interview quality; nevertheless, note-taking and probing questions have resulted in collecting meaningful data on patient experiences consistent with study aims. In this single-centre study, the findings presented are geographically limited and may not be transferable to other regions of the UK or countries, particularly where protocols and scope of practice may differ. While the sample size was small, it is consistent with models of qualitative research,[29] and data saturation was assumed, given that no new information related to the themes was found in the final interviews. A wider sample may be reached through the use of a standardised questionnaire. However, a thorough description of the research context and sufficient data collected through in-depth interviews was presented, to allow readers to assess whether the findings are transferable to their context.

CONCLUSION

Ocular pain was a widely reported side-effect in many but not all anti-VEGF injections, with soreness and irritation commonly reported to last for up to 36 hours affecting patient recovery. Practitioners should adapt pain assessment tools to evaluate the patient experience during and following each injection and deliver ongoing information to support patients in managing pain at home. Generally, patients recognised that adherence to treatment was essential to reduce the risk of further vision loss.

Twitter Heather Waterman @N/A

Acknowledgements We are grateful to the hospital eye clinic staff and to all study participants.

Contributors CY, JHA, SB, HW and AW contributed to the design and development of the study protocol. AW secured funding. CY collected, transcribed and analysed the interview data, and themes and subthemes were settled on by discussion with JHA, HW and AW. The write-up was led by CY, with feedback and guidance in developing the manuscript provided by JHA, HW and AW. All authors read and approved the final manuscript. AW is the guarantor of this work.

Funding The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: this work was supported by the Abbeyfield Research Foundation (grant number: 472).

Competing interests None declared.

Patient and public involvement The research question and study design was informed by patient views elicited from feedback of a local patient group with

macular disease. Fourteen patients participated in this study, a summary of study results was sent to all participants who requested it.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the National Health Service Wales and the South East Wales Research Ethics Committee (19/WA/0004). The study was based on the principles stated in the Declaration of Helsinki and written informed consent was gained from each participant.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article.

ORCID iDs
Jennifer H Acton http://orcid.org/0000-0002-0347-7651
Ashley Wood http://orcid.org/0000-0002-9312-6184

REFERENCES

1 Wong WL, Su X, Li X, *et al*. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health* 2014;2:e106–16.
2 Ambati J, Fowler BJ. Mechanisms of age-related macular degeneration. *Neuron* 2012;75:26–39.
3 Taylor DJ, Hobby AE, Binns AM, *et al*. How does age-related macular degeneration affect real-world visual ability and quality of life? A systematic review. *BMJ Open* 2016;6:e011504.
4 Maguire MG, Martin DF, Ying G-shuang, Ying G, *et al*. Five-Year outcomes with anti–vascular endothelial growth factor treatment of neovascular age-related macular degeneration. *Ophthalmology* 2016;123:1751–61.
5 Boyle J, Vukicevic M, Koklanis K, *et al*. Experiences of patients undergoing repeated intravitreal anti-vascular endothelial growth factor injections for neovascular age-related macular degeneration. *Psychol Health Med* 2018;23:127–40.
6 Sii S, Aspinall P, Borooah S, *et al*. Exploring factors predicting changes in patients' expectations and psychosocial issues during the course of treatment with intravitreal injections for wet age-related macular degeneration. *Eye (Lond)* 2018;32:673–8.
7 The Royal College of Ophthalmologists. Commissioning guidance - age related macular degeneration services. 2021. Available: https://www.rcophth.ac.uk/resources-listing/commissioning-guidance-age-related-macular-degeneration-services/ [Accessed 22 May 2023].
8 Mitchell P, Korobelnik J-F, Lanzetta P, *et al*. Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials. Br J Ophthalmol 2010;94:2–13.
9 Rufino S, Berta A, Larsen M. Treat-and-extend versus monthly regimen in neovascular age-related macular degeneration: results with ranibizumab from the trend study. Ophthalmology 2018;125:57–65.
10 Kertes PJ, Galic IJ, Greve M, *et al*. Efficacy of a treat-and-extend regimen with ranibizumab in patients with neovascular age-related macular disease: a randomized clinical trial. *JAMA Ophthalmol* 2020;138:244–50.
11 The Royal College of Ophthalmologists. Ophthalmic service guidance - intravitreal injection therapy. 2018. Available: https://www.rcophth.ac.uk/wpcontent/ uploads/2018/02/Intravitreal-Injection-Therapy-August-2018-2.pdf [Accessed 25 Jan 2018].
12 Katz J, Melzack R. Measurement of pain. *Surg Clin North Am* 1999;79:231–52.
13 Yau GL, Jackman CS, Hooper PL, *et al*. Intravitreal injection anesthesia-comparison of different topical agents: a prospective randomized controlled trial. *Am J Ophthalmol* 2011;151:333–7.
14 Davis MJ, Pollack JS, Shott S. Comparison of topical anesthetics for intravitreal injections: a randomized clinical trial. *Retina* 2012;32:701–5.
15 Ratnarajan G, Nath R, Appaswamy S, *et al*. Intravitreal injections using a novel conjunctival mould: a comparison with a conventional technique. *Br J Ophthalmol* 2013;97:395–7.
16 Moisseiev E, Regenbogen M, Bartfeld Y, *et al*. Evaluation of pain in intravitreal bevacizumab injections. *Curr Eye* Res 2012;37:813–7.
17 Rodrigues EB, Grumann A Jr, Penha FM, *et al*. Effect of needle type and injection technique on pain level and vitreal reflux in intravitreal injection. *J Ocul Pharmacol Ther* 2011;27:197–203.
18 Haas P, Falkner-Radler C, Wimpissinger B, *et al*. Needle size in intravitreal injections - pain evaluation of a randomized clinical trial. *Acta Ophthalmol* 2016;94:198–202.
19 Tailor R, Beasley R, Yang Y, *et al*. Evaluation of patients' experiences at different stages of the intravitreal injection procedure - what can be improved *Clin Ophthalmol* 2011;5:1499–502.
20 Chua PYS, Mitrut I, Armbrecht A-M, *et al*. Evaluating patient discomfort, anxiety, and fear before and after ranibizumab Intravitreous injection for wet age-related macular degeneration. *Arch Ophthalmol* 2009;127:939–40.
21 Finger RP, Wiedemann P, Blumhagen F, *et al*. Treatment patterns, visual acuity and quality-of-life outcomes of the WAVE study - a noninterventional study of ranibizumab treatment for neovascular age-related macular degeneration in Germany. *Acta Ophthalmol* 2013;91:540–6.
22 Obeid A, Gao X, Ali FS, *et al*. Loss to follow-up among patients with neovascular age-related macular degeneration who received intravitreal anti-vascular endothelial growth factor injections. *JAMA Ophthalmol* 2018;136:1251–9.
23 Thetford C, Hodge S, Harding S, *et al*. Living with age-related macular degeneration treatment: patient experiences of being treated with ranibizumab (Lucentis) (R) intravitreal injections. Br J Vis Impair 2013;31:89–101.
24 Thier A, Breuning M, Wolfram C, *et al*. Emotional and physical experiences of people with neovascular age-related macular degeneration during the injection process in Germany: a qualitative study. *BMJ Open* 2022;12:e058266.
25 McCloud C, Lake S. Understanding the patient's lived experience of neovascular age-related macular degeneration: a qualitative study. *Eye (Lond)* 2015;29:1561–9.
26 Burton AE, Shaw R, Gibson J. Experiences of patients with age-related macular degeneration receiving anti-vascular endothelial growth factor therapy: a qualitative study. Br J Vis Impair 2013;31:178–88.
27 Merriam SB. *Qualitative research and case study applications in education*. San Francisco: Jossey-Bass Publishers, 1998: 5–6.
28 Creswell JW, Guetterman TC. Principles and approaches in qualitative health research. In: *Educational research: planning, conducting, and evaluating quantitative and qualitative research*. 2018: 3–112.
29 Green J, Thorogood N. Qualitative methods for health research. 4th Edition. SAGE Publications Ltd, 2018.
30 Etikan I. Comparison of convenience sampling and purposive sampling. *AJTAS* 2016;5:1.
31 Braun V, Clarke V. Reflecting on reflexive thematic analysis. Qual Res Sport Exerc Health 2019;11:589–97.
32 Francis JJ, Johnston M, Robertson C, *et al*. What is an adequate sample size? Operationalising data saturation for theory-based interview studies. *Psychol Health* 2010;25:1229–45.
33 Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3:77–101.
34 Carter N, Bryant-Lukosius D, DiCenso A, *et al*. The use of triangulation in qualitative research. *Oncol Nurs Forum* 2014;41:545–7.
35 O'Brien BC, Harris IB, Beckman TJ, *et al*. Standards for reporting qualitative research: a synthesis of recommendations. *Acad Med* 2014;89:1245–51.
36 Papanikolaou T, Islam T, Hashim A. Tolerability and safety profile of povidone iodine in pre-operative kin and eye disinfection prior to intraocular surgery. *J Clinic Experiment Ophthalmol* 2011;2:1–3.
37 Pang CE, Mrejen S, Hoang QV, *et al*. Association between needle size, postinjection reflux, and intraocular pressure spikes after intravitreal injections. *Retina* 2015;35:1401–6.
38 Lerebours VC, Nguyen T-G, Sarup V, *et al*. Intravitreal injection-induced migraine headaches. *Cureus* 2016;8:e561.

39 Finset A. How communication between Clinicians and patients may impact pain perception. In: *placebo and pain: from bench to bedside*. Elsevier, 2013: 243–56.
40 Sanabria MR, Montero JA, Losada MV, *et al*. Ocular pain after intravitreal injection. *Curr Eye* Res 2013;38:278–82.
41 Lindsell L, Miller D, Brown J. Use of topical ice for local anesthesia. JAMA Ophthalmol 2015;132:2014–5.
42 Besirli CG, Smith SJ, Zacks DN, *et al*. Randomized safety and feasibility trial of ultra-rapid cooling anesthesia for intravitreal injections. *Ophthalmol Retina* 2020;4:979–86.
43 Zinkernagel MS, Schorno P, Ebneter A, *et al*. Scleral thinning after repeated intravitreal injections of antivascular endothelial growth factor agents in the same quadrant. *Invest Ophthalmol Vis Sci* 2015;56:1894–900.
44 Flaxel CJ, Adelman RA, Bailey ST, *et al*. Age-related macular degeneration preferred practice pattern®. *Ophthalmology* 2020;127:1–65.
45 Gambrell J, Schaal S. Topical anesthesia for intravitreal injection. *Expert Opin Drug Deliv* 2012;9:731–3.
46 Martindale A. *Martindale: the complete drug reference*. London, 2017.
47 Segal O, Segal-Trivitz Y, Nemet AY, *et al*. Anxiety levels and perceived pain intensity during intravitreal injections. *Acta Ophthalmol* 2016;94:203–4.
48 Rhudy JL, Meagher MW. Fear and anxiety: divergent effects on human pain thresholds. *Pain* 2000;84:65–75.
49 Folk J. Eye problems, vision anxiety symptoms. Available: www.anxietycentre.com. 2020.https://www.anxietycentre.com/anxiety-symptoms/eye-vision-problems.shtml [Accessed 3 Mar 2020].
50 Lazarus RS. Progress on a cognitive-motivational-relational theory of emotion. *Am Psychol* 1991;46:819–34.
51 Stephen S, Nesbit S. Diagnosis and treatment planning in dentistry. 3rd ed. Elsevier, 2016.
52 Dang BN, Westbrook RA, Njue SM, *et al*. Building trust and rapport early in the new doctor-patient relationship: a longitudinal qualitative study. *BMC Med Educ* 2017;17:32.