East and North Hertfordshire treatment pathway for primary open angle glaucoma and ocular hypertension in adults

Introduction

Glaucoma is a group of eye diseases causing optic nerve damage. In most cases of glaucoma, increased intraocular pressure plays a role in damaging the fragile nerve fibers. When sufficient nerve fibers are damaged, blind spots develop in the visual field. This damage is irreversible. Due to overlapping visual fields often patients only becomes symptomatic when there is considerable damage. Glaucoma is a leading cause of blindness in the western world.

Ocular hypertension is not the same as glaucoma. It is often considered a precursor to glaucoma. In ocular hypertension, the optic nerve is still normal and no other signs of glaucoma are found and the pressure in the eye is higher than that in the general population. However, people with ocular hypertension are more likely to develop glaucoma and should be monitored and treated if they are at high risk.

For glaucoma, after accurate diagnosis, therapy is normally initiated with a prostaglandin analogue eye drop. If there is insufficient control, then various other classes of drugs can be added to the therapy. Clear information on compliance is required. There are options regarding laser therapy and various surgical options can be considered.

Eye drops come in various forms. There are drops that contain a single active ingredient, drops that contain fixed combinations of ingredients. These drops maybe generic or could be under license. They can be preserved, they may have dissipating preservatives or maybe preservative free.
Types of glaucoma

Primary open-angle glaucoma

Primary open-angle glaucoma is the most common form of glaucoma. It can be thought of that the eye has an internal 'hydraulic' system aimed at keeping the eye 'inflated'. The eye produces fluid and needs to drain the fluid out of the eye. This has nothing to do with tear production. The angle where the fluid leaves the internal component of the eye is normally in an 'open' configuration. The fluid drains through a sponge like material. If there is an imbalance between fluid production and drainage i.e. where either too much is produced or too little draining out, then there will be a relative increase in the intraocular pressure. This is known as primary open angle glaucoma.

Other forms of glaucoma:

- Angle-closure glaucoma
- Normal tension glaucoma
- Pseudoexfoliation syndrome
- Pigmentary glaucoma
- Congenital glaucoma
- Secondary glaucoma - including previous trauma, tumors, and other eye diseases.

Guidelines

The ophthalmology service follows NICE guidelines on the diagnosis, monitoring and treatment of open-angle glaucoma. The European Glaucoma Society guidelines as well as treatment pathways from a number of other NHS trusts have been reviewed in the development of this pathway.

Therapy - eye drops

A. Individual therapy:

NICE guidelines 2009 - recommend a prostaglandin analogue as first-line treatment in primary open angle glaucoma. Beta blocker is commonly recommended as second line therapy, as long as there are no recognised contraindications. The other treatment classes include carbonic anhydrase inhibitors, sympathomimetics and mitotics.

Prostanoids (Prostaglandin Analogues & Prostamides) eg latanoprost, bimatoprost, travoprost:
There are 3 commonly prescribed options. **Latanoprost** is currently available as a generic, **Travoprost** will soon be available as a generic (May 2017) and **Bimatoprost** 0.1% that has a patent valid until June 2017. Bimatoprost is not a prostaglandin analogue, rather it is a prostamide with a better pressure lowering action. These drops are commonly associated with some mild side-effects such as; stinging on installation, discolouration of the iris and periocular tissue as well as elongation of the lashes.

**Beta blockers eg timolol:**

There has been a recent move away from beta-blockers as a second-line therapy in the very elderly. These have a well-recognised side-effect and contraindication profile. This includes; low blood pressure, reduced pulse rate, fatigue, shortness of breath; rarely: reduced libido, depression.

**Sympathomimetics eg brimonidine:**

May cause burning or stinging, fatigue, headache, drowsiness, dry mouth and nose, relatively higher likelihood of allergic reaction.

**Carbonic Anhydrase Inhibitors eg brinzolamide, dorzolamide, acetazolamide (oral):**

This is available in eye drop form with possible symptoms of stinging, burning, eye discomfort. In oral form (acetazolamide) the side effects may include tingling hands and feet, fatigue, stomach upset, memory problems, frequent urination.

**B. Compliance:**

A very crucial step in managing glaucoma is ensuring compliance with eye drop installation. Compliance aids are available for a number of the drops. These help improve the accuracy of getting the drop into the eye and reducing excessive delivery of the drops - this results in patients running out of drops before the end of the month.

**C. Combination drops:**

It is considered good practice that individual eyedrops are used unless compliance is an issue. The advantage of combination drops is that it reduces the number of different bottles being used, improving compliance. Additionally there is less volume of preservatives instilled in the eyes. The success of glaucoma surgery is negatively impacted if a patient had previously used many preservative containing drops.
D. Preservatives:

Many drops are preserved with Benzalkonium chloride (Quaternary Ammonium). There has been increased recognition of the cytotoxic action of this preservative to the ocular surface. For some patients, this preservative results in a significant degree of toxic damage to the ocular surface resulting in patient intolerance with the therapy. The toxic damage is not limited to the ocular surface but may affect the trabeculum, lens and retina with an increased incidence of cataract related macular oedema. Toxic damage is aggravated with any underlying disease such as dry eye disease.

Some patients may have a direct allergy to this preservative however the allergy may be in response to the active drug. With regards to glaucoma therapy the only preservative free options are formulations in single dose units.

Allergic reactions can cause: eyes and eyelids to itch severely; eyes to become red and injected; eyelids to become red and swollen. Symptoms and signs become worse after the drops are instilled, and they resolve when treatment is stopped. Ophthalmologist makes the diagnosis. Refer to POAG/OHT and Allergy/Toxicity Guideline sections for guidance on treatment options.

E. Generic eye drops

From a cost perspective fortunately a number of drops have become available as generic therapies. Eye drops will always be firstly prescribed as a generic. However there are a number of confounding issues with generic eye drops that are important to consider. Patients and their doctors must work together to ensure that the generic drops are achieving the desired result.

Confounding factors with generic therapy include:

1. **Therapeutic equivalence** – Concerns have been raised about the therapeutic equivalence of branded vs generic eye drops. There is some evidence that appears to demonstrate inferiority of certain generic products whereas there is also evidence that demonstrates no difference. With generics bioequivalence needs to be shown but not therapeutic equivalence. In the eye bioequivalence can't be easily assessed. Minor formulation differences may affect how well the active ingredient is absorbed.

2. **Design of the bottle** - difficult to squeeze with poor drop delivery or too easy to squeeze with squirting of the drops

3. **Size of the eye drop** - this will vary with each manufacturer and effects how long a container will last.
4. **Storage of the bottle** - some bottles are light-sensitive, some bottles of temperature-sensitive, some bottles are both light and temperature sensitive, and some bottles are not sensitive and can be stored next to the bed. As patients may get a bottle form a different generic manufacturer each month, it must be made clear to them each month what the storage instructions are for that specific generic bottle.

5. **Compliance** - The active ingredient needs to be the same in a generic not the inactive ingredients. This can affect the pH of the drops which may make the drops feel less comfortable in a patient's eye ultimately affecting compliance.

*Eye drops will routinely be prescribed generically. However, if upon review and monitoring there is evidence of progression of disease, poor or fluctuating control of the intraocular pressure, increased side effects or an inability to administer the eye drops correctly consideration will be given to the eye drop product(s) being used. Consideration will be given to prescribing a specific branded generic or branded therapy where appropriate.*

**Therapy - laser / surgery**

**Laser:**

There has been an increase in the popularity of a minimally invasive laser therapy such as selective laser trabeculoplasty. NICE Clinical Knowledge Summaries on Glaucoma (January 2016) states "Selective laser trabeculoplasty is often as effective as medical therapy to achieve target intraocular pressures. Selective laser trabeculoplasty is therefore gaining in popularity as a first-line treatment." Selective laser trabeculoplasty efficacy reduces with the increase number of drops a patient is using.

Selective laser trabeculoplasty involves a low-energy laser aimed at the trabecular meshwork. It is thought to work by selectively targeting melanin pigment which occurs in a proportion of cells in the trabecular meshwork. This increases the drainage capacity of the trabecular meshwork but causes little damage to the structures there. Therefore, if needed, it can be safely repeated. It often needs to be repeated between every three and five years.

There are other forms of laser also available for open-angle glaucoma including Argon laser trabeculoplasty and micropulse laser trabeculoplasty however these are technically more difficult to perform and less commonly used.

**Surgery:**

Trabeculectomy is a well-known and practiced surgery technique for glaucoma. Recently there has been a significant increase in the availability of various small drainage shunts that can be inserted to improve the outflow of fluid from the eye.
Pathway - Principles

- This pathway applies to newly diagnosed adults and existing patients requiring a therapy change
- The principles within the NICE glaucoma guidelines including measurement of the central corneal thickness (CCT) are followed
- There is increasing recognition of Beta blocker side effects especially in the elderly and hence they are no longer considered a 1st line option
- The ophthalmology service advocates an increasing role of Selective Laser Trabeculoplasty (SLT)
- Costs are an important consideration
- Stress compliance and education on instilling drops before changing treatment.
- Look for a single spike in IOP in a normally well controlled patient. Consider compliance / review rather than immediate change in therapy
- Single component drops are used, rather than fixed combinations, unless on 3 or more therapies
- If there is no response first confirm compliance and installation technique before changing therapy
- If no IOP reduction on one therapy, change therapy rather than just adding a new drop
- If there is an initial response to the Prostanoid, but it is inadequate, then add in a second line therapy.

OHT and POAG principles:

- 1st line generic Latanoprost
- 2nd line Bimatoprost 0.1%
- If there is an initial response to the Prostanoid, but it is inadequate, then add in a second line therapy (carbonic anhydrase inhibitor, sympathomimetic, beta-blocker).
- Further treatment options for clinicians (more than one agent may be needed concurrently to achieve target IOP) – see below for alternative therapies
- Consider SLT (Selective Laser Trabeculoplasty) if:
  - eye drops are contraindicated/not tolerated
  - there is inability to administer eye drops appropriately
  - concordance to eye drops is poor
  - the addition of a 3rd eye drop concurrently would be required
  - preservative free eye drops are required
POAG / OHT Guideline:

Eye drop costs stated are for 1 month treatment prescribed generically (Drug Tariff Jan 2017)

Prostaglandin

1. Latanoprost 50micrograms/ml eye drops, 2.5ml - £1.40
2. Bimatoprost 100micrograms/ml eye drops, 3ml - £11.71

Carbonic anhydrase Inhibitor

3. Dorzolamide 20mg/ml eye drops, 5ml - £1.90
4. Brinzolamide 10mg/ml eye drops, 5ml - £2.11

Laser

5. Consider SLT (see notes above)

Sympathomimetic

6. Brimonidine 0.2% eye drops, 5ml - £1.66

7. Timolol (0.25% eye drops, 5 ml - £1.43 and Combinations – see table (consider combination products if on 3 or more therapies)

Table 1 – fixed combinations for preserved eye drops

<table>
<thead>
<tr>
<th>pharmacological treatment class</th>
<th>pharmacological treatment combination</th>
<th>Brand name</th>
<th>Monthly cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGA &amp; BB</td>
<td>Latanoprost 50micrograms/ml / Timolol 5mg/ml eye drops</td>
<td>Generic</td>
<td>£2.07</td>
</tr>
<tr>
<td>PGA &amp; BB</td>
<td>Bimatoprost 300micrograms/ml / Timolol 5mg/ml</td>
<td>Ganfort</td>
<td>£13.95</td>
</tr>
<tr>
<td>CAI &amp; BB</td>
<td>Dorzolamide 20mg/ml / Timolol 5mg/ml</td>
<td>Generic</td>
<td>£1.81</td>
</tr>
<tr>
<td>CAI &amp; BB</td>
<td>Brinzolamide 10mg/ml / Timolol 5mg/ml</td>
<td>Azarga</td>
<td>£11.05</td>
</tr>
<tr>
<td>Alpha 2 &amp; BB</td>
<td>Brimonidine 2mg/ml / Timolol 5mg/ml</td>
<td>Combigan</td>
<td>£10.00</td>
</tr>
<tr>
<td>CAI &amp; Alpha 2</td>
<td>Brinzolamide 10mg/ml / Brimonidine 2mg/ml</td>
<td>Simbrinza</td>
<td>£9.23 (higher cost than if prescribed separately)</td>
</tr>
</tbody>
</table>

PGA - prostanoid; BB - beta-blocker; Alpha 2 - alpha2-adrenoceptor agonist (sympathomimetic)

8. Surgery
For Allergic or toxic reactions:

- Can be allergic to preservatives or to the active ingredient
- Allergy - “Itch, relieved when stopping using the drops”
- Ophthalmologist makes the diagnosis
- OHT or Glaucoma suspect - only give (expensive preservative free) therapy where at high risk of glaucoma.
- If not high risk withdraw (expensive preservative free) therapy as is not cost effective. Patients will continue to be re-assessed for treatment

**Allergy / Toxicity Guidelines**

- Consider SLT (see above)
- Latanoprost 50micrograms/ml eye drops 0.2ml unit dose preservative free (Monopost - £8.49)
- If inadequate control add Timolol 1mg/g gel eye drops 0.4g unit dose preservative free (Tiopex once daily (£7.49) (vs timolol (Timoptol) 0.25% or 0.5% eye drops 0.2ml unit dose preservative free £16.90 (0.25%) or £19.30 (0.5%))
  - If BB is contraindicated or for high risk glaucoma patients then use CAI - Dorzolamide 2% eye drops 0.2ml unit dose preservative free (Trusopt) (£24.18)
- If control is still inadequate then stop the Tiopex and switch to PF CAI & BB = Dorzolamide 2% / Timolol 0.5% eye drops 0.2ml unit dose preservative free (Cosopt) (£28.59)
- Other options:
  - PGA - Bimatoprost 300micrograms/ml eye drops 0.4ml unit dose preservative free (Lumigan) - £13.75
  - PGA & BB - Bimatoprost 300micrograms/ml / Timolol 5mg/ml eye drops 0.4ml unit dose preservative free (Ganfort) (£17.50)
- Then surgery
Figure 1 – NICE OHT guidelines – note where beta-blocker stated above in box 7 prostaglandin analogues are used 1st line instead.

Reference:
2. NICE Glaucoma: diagnosis and management Clinical guideline [CG85] Published date: April 2009 https://www.nice.org.uk/guidance/cg85
3. NICE Clinical Knowledge Summaries on Glaucoma (January 2016) https://cks.nice.org.uk/glaucoma