Case Record 4

ADRs and the Eye, Yellow Cards, Optometrists' Roles and Sildenafil

June 2012

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Introduction
Adverse Drug Reactions and Optometry Evolution

Even if it were feasible to learn, by rote, all ocular side effects, real, theoretical and synergistic, of every drug, the exercise would be fruitless. MHRA (2008) reports approximately 5000 new licences are granted for medicines or devices each year; knowledge is diluted almost immediately. Reference tomes such as 'Meyler's Side Effects of Drugs: the International Encyclopaedia of Adverse Drug Reactions and Interactions' (Aronson 2006) or the optometry targeted emedINFO (Thomson and Lawrenson 2009) could be accessed.

Caution however is essential as there are omissions.

For Keratoconjunctivitis Sicca, neither Meyler nor emedINFO include Detrusitol. A strong antimuscarinic drug licensed for the treatment of Urge Incontinence, the Summary of Product Characteristics (SPC) (Pharmacia 2012) and the BNF (2012) specifically state 'Dry Eye' as a possible side effect. Intuitively this should seem probable considering the drug's pharmacological mechanism and purpose.

Inconsistencies are also evident; the two reference documents do not unanimously agree. Retinal detachment is a very significant ocular side effect of oral contraceptives highlighted in Meylers, but not recognised in emedINFO.

Finally these reference resources do not necessarily provide information on the relative incidences of side effects.
Drug side effects are rated in product literature with quantified frequencies as Very Common (1 in 10), Common (1 in 10 to 1 in 100), Uncommon (1 in 100 to 1 in 1000, Rare (1 in 1000 to 1 in 10000) and Very Rare (<1 in 10000) (BNF 2012). However the effects themselves can be descriptively imprecise and appear to reflect the way adverse reactions would be reported by lay persons via the Yellow Card system. Amongst the ocular adverse reactions listed in the SPC for Viagra (Pfizer 2010) are Visual Disorders (Common), and Conjunctival Disorders, Eye Disorders, Lacrimation Disorders, Other Eye Disorders (Uncommon), none of which carry any diagnostic meaning. Adding to the nebulous nature of drug information, the following statement was extracted from the SPC of Cerazette, a common oral contraceptive, prior to an update on 29/3/12: 'The undesirable effects mentioned in the table below have been

judged, by the investigators, as having an established, probable, or ***possible*** (bold italics added) link to the treatment'.

Reliance solely on published reference literature would seem less than ideal.
This is not a rationale to abdicate responsibility. However, clinicians must be circumspect and use personal clinical judgement, based on habitual, repetitive practice to guide interpretation of often vague and sometimes contradictory evidence. The evolution of optometrists into mainstream primary care clinicians necessitates a mandatory, effective and meaningful medical and drug history, including allergies, be elicited from every patient. Assimilation of real life information via patients is essential both medically and educationally; taking a drug inventory without a frame of reference serves no purpose. Apart from building patient rapport, an intuitive feel for commonly used drugs can be quickly developed making peculiar reactions more easily distinguishable from the clinical noise.

All drugs have side effects (MHRA 2008). The questions are how serious or likely is the side effect and is it only in overdose or at therapeutic levels.
Ethambutol, Vigrabatrin, Desferroximine and Hydroychloroquine are the four primary drugs potentially causing significant and often irreversible adverse ocular effects at therapeutic levels; requiring screening protocols to detect drug effects (Lai et al 2007, Aaronson 2006). While Vigrabatrin and Hydroxychloroquine are encountered relatively frequently, most drugs encountered in primary care have far less dramatic or predictable interactions.
Amitriptyline is a commonly encountered drug; a tri-cyclic antidepressant licensed for depressive illness and enuresis in children (Actavis 2011), it is also routinely prescribed for chronic neuropathic pain (bnf 2012) and migraine prophylaxis (SIGN 2008). Listed as a special warning in the summary of product characteristics (Actavis 2011), therapeutic doses can, due to an antimuscarinic effect, elicit closed angle glaucoma. The frequency is not mentioned but general knowledge of the use of this drug suggests the possibility is exceptionally unlikely. An optometrist should be more conscious of physical signs of narrow angles that may make the patient susceptible regardless of drug triggers.

Conversely, and irrespective of statistical probabilities, clinical experience can help inform suspicion of idiosyncratic reactions that may not be recorded.

April 2002

Salient information taken from electronic records

DATE: 4/4/02

Mr Age : 60.
Address

Presenting Symptoms
Flashing lights, particularly on bending. Vision seems stable.

POH
Bifocals. No previous ocular surgery or treatments.

FOH
Nil.

General Health and Medications
Non-smoker. No allergies, No hayfever
Sildenafil – for approximately one month
Nasal Infection - Naseptin (Chlorhexidone/Neomycin) Cream
No other medications : General health good.
No previous history of general or ocular medication use or surgery.

Refraction

R -2.00/-2.50x90 (6/5)	Add +2.25 N5
L -3.25/-1.75x70 (6/5)	Add +2.25 N5

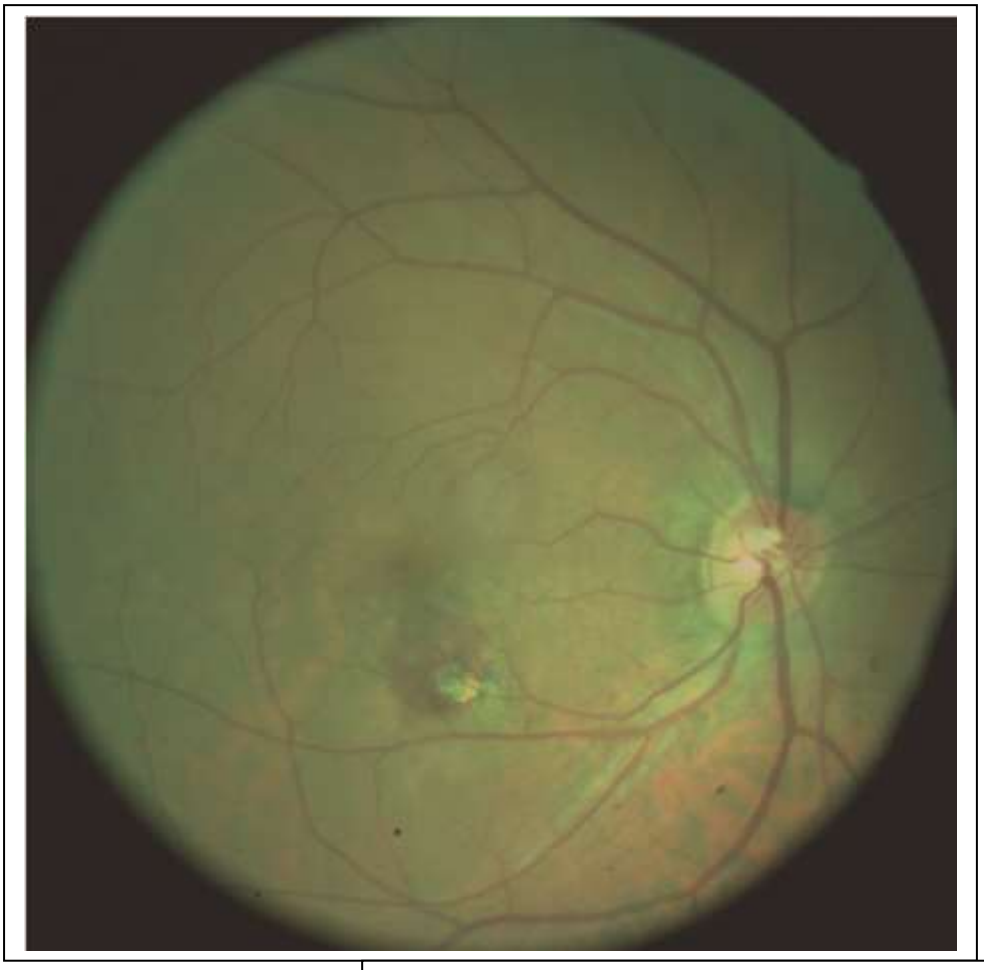
Tensions (GAT) (12.35pm) R 17 L 19

Amsler R Distortion, L NAD

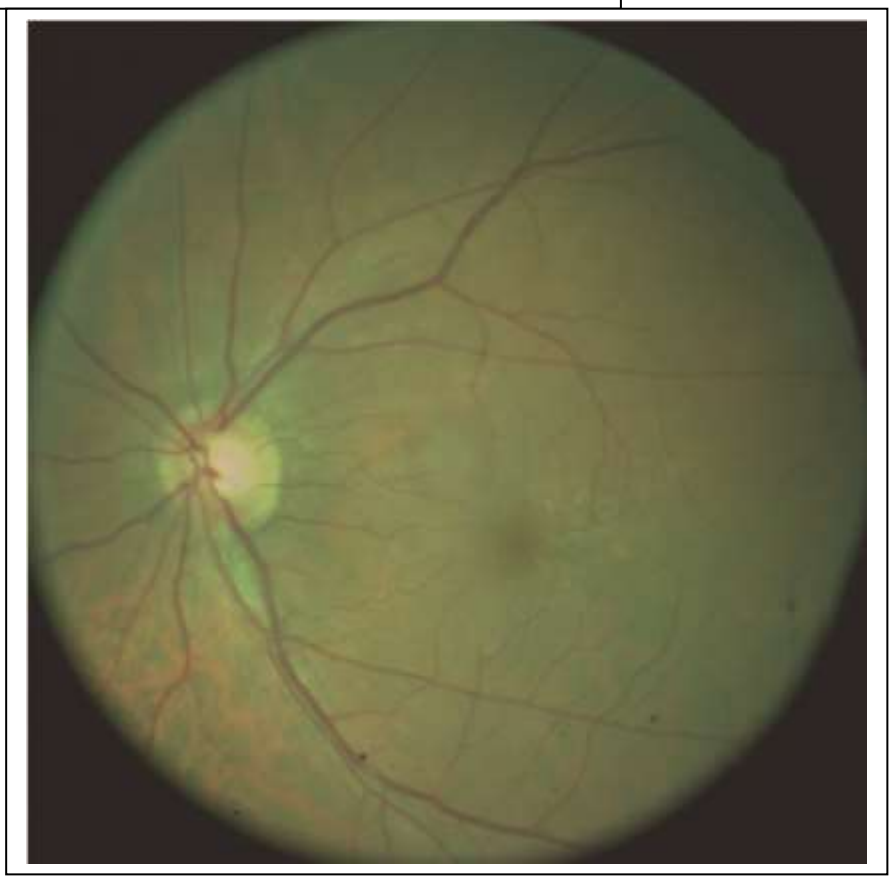
Pupils E&A D,C& N

Dilated Fundsocopy (1.0% Tropicamide)

RIGHT CD 0.3 rims good, no bayoneting, no baring. Neural rims healthy. Perimacular intraretinal haemorrhage inferior to macula.



LEFT VCD 0.5 Rims good, no bayoneting, no baring.
Macula drusen – flat.



Advice and CMP
Urgent referral to ophthalmology.

February 2003

Salient information taken from electronic records
DATE: 20/2/03

Mr Age : 61.
Address

Presenting Symptoms
Routine, discharged from HES, VA in RE now poor – Not happy with causes or outcome. Feels Sildenafil caused problem, reported to GP. Stopped Sildenafil voluntarily as a consequence.

POH
Exudative AMD 2002. Discharged from HES.

FOH
Nil.

General Health and Medications
Non-smoker. No allergies, No Hayfever
No current medications – voluntarily stopped Sildenafil.
General health good.
Exudative AMD RE. LE - Drusen.

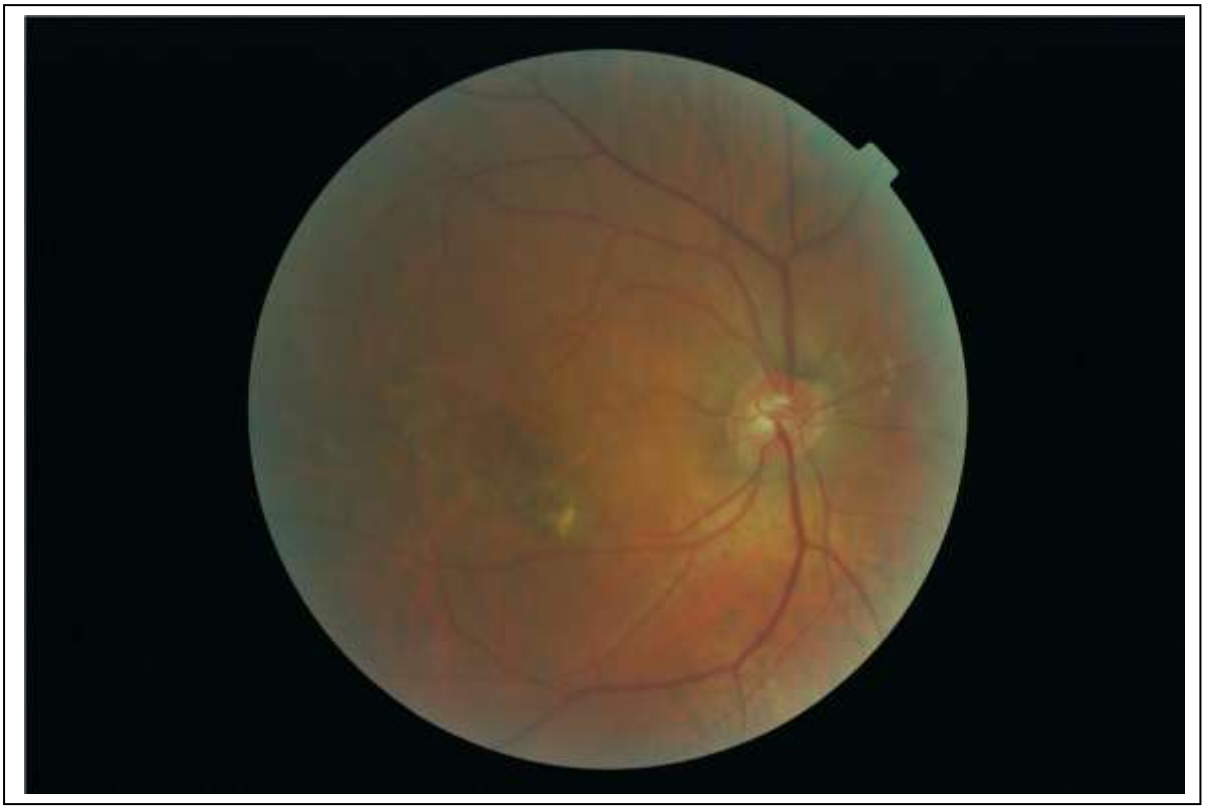
Refraction

R -2.25/-2.75x95 (6/24)	Add +2.50 N14
L -3.00/-2.25x70 (6/4.8)	Add +2.50 N5

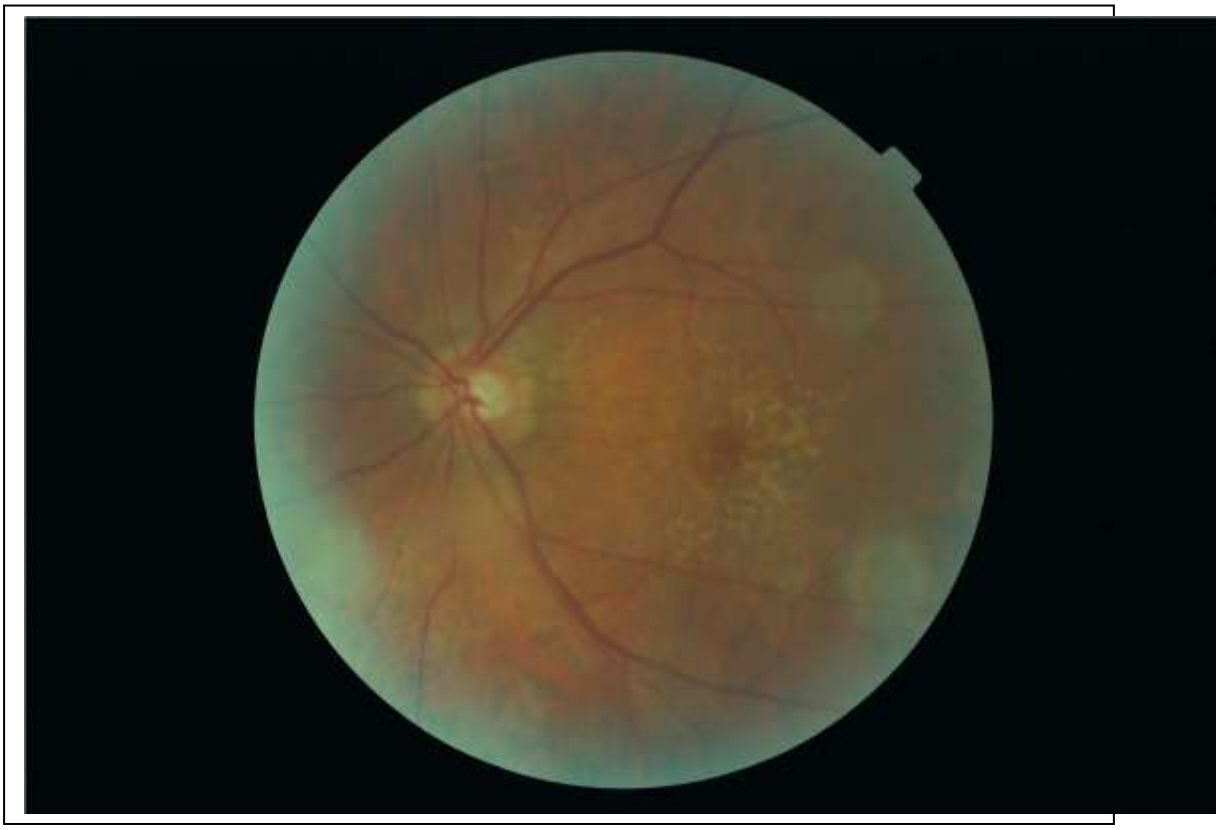
Tensions (GAT) (12.35pm) R 18 L 17

Pupils E&A D,C& N

Dilated Fundsocopy (1.0% Tropicamide)
RIGHT CD 0.3 rims good, no bayoneting, no baring. Neural rims healthy. Retinal scar inferior to macula - flat



LEFT VCD 0.5 Rims good, no bayoneting, no baring.
Hard macula drusen – flat.



Advice and CMP
Yellow Card for Sildenafil and Exudative AMD discussed. Decision to co-write Yellow Card scheme via electronic BNF instigated.
Home Amsler, nutritional information and warning signs explained - invitation to return if deterioration in the left eye.

Discussion

Anecdotal evidence in isolation is of little value. However the MHRA receives, via the Yellow Card system, 20,000 anecdotal reports of suspect drug reactions per year (MHRA 2008). The system constitutes a structured way of amalgamating and analysing, perhaps disparate, pieces of information (BNF 2012), and represents continuous and ongoing arbitration of drug performance.

Exact drug mechanisms are not always known, regardless of the effects witnessed and the outcomes marketed. Sildenafil is a selective inhibitor of phosphodiesterase 5 (Dale et al 2000) and was originally developed to reduce blood pressure via augmentation of renal tubular activity (Barnett and Machado 2006). These authors indicate that the coincidental finding Sildenafil induces vasodilation and platelet inhibition turned attention toward the possible role of this drug for the treatment of angina. The beneficial effect on erectile dysfunction was completely unexpected and unplanned. Pfizer (2007) indicate that Sildenafil has no direct relaxant effect on the corpus cavernosum but rather has an indirect effect on the nitric oxide (NO) pathway and Barnett and Machado (2006) imply that an understanding of the mechanism of action of Sildenafil was only clarified after the observed effects on human beings.
Even after Phase III trials, unexpected drug effects, if not probable, are certainly possible; the Yellow Card system is designed to retrieve relevant evidence.

NO is a potent vasodilator and endothelium relaxing factor as well as an inhibitor of platelet aggregation (Kimura and Esumi 2003). Schmetterer and Polak (2001) further emphasise this role of NO in the optic nerve, choroid and retina, while Kimura and Esumi (2003) comment that NO acts as a trigger for vascular endothelial growth factor (VEGF).

Pfizer (2010) suggests there is no safety information on the use of Sildenafil in patients with bleeding disorders but warn that careful assessment of risk should be made. Further, BNF (2012) lists painful red eyes, flushing and epistaxis as possible side effects.

Coupled with the documented effects of NO within the eye would suggest the possibility of an exudative retinal event, especially in a predisposed individual. In this case the patient had pre-existing atrophic macula degeneration. Prall (2012) indicates that 10 to 20% of patients with atrophic AMD will progress to the exudative form so the haemorrhagic event for this patient may have been coincidental to Sildenafil but the possibility still needed consideration.

Cardiovascular haemorrhage and transient ischaemic attack, hypertension and hypotension have been reported via the Yellow Card system for Viagra (Pfizer 2010). The SPC (Pfizer 2010) notes that most patients reporting these reactions had pre-existing risk factors and concluded the determination of a direct cause and effect not possible. Regardless the incidents are significant enough for Pfizer to include the possibilities within the SPC data.
Likewise AMD may be a contributing risk factor.

The patient had been using Sildenafil for approximately a month prior to the retinal event. Erectile dysfunction, cardiovascular disease, diabetes, hyperlipidaemia and smoking often coexist (Webb et al 1999); some are also potential risk factors for exudative AMD (Prall 2012). This patient was in good health, was not on any general health medications and did not smoke, but did have pre-existing atrophic AMD. The time course was discussed with the gentleman and while the likelihood of this episode reflecting a true cause and effect was considered unlikely, it was deemed important enough to report; accessed via the Yellow Card section of the electronic BNF.

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The original referral was in 2002, prior to anti-VEGF treatments. The resultant reduction in vision in the right eye was profound. The patient still needs no general health medications and ocular status remains unchanged. The most recent update of the SPC for Viagra (Pfizer 2010) does not include a possibility of exudative AMD as an adverse drug reaction. The reporting of this event has obviously not been supported by similar incidents and must be considered an unrelated episode.

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