The role of optical coherence tomography in therapeutics and conditions, which primarily have systemic manifestations: a narrative review

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Abstract: Optical coherence tomography is designed to evaluate *in vivo* qualitative and quantitative changes of the anterior segment, optic nerve and the retina. Initial applications of this technology were confined mainly to ophthalmic diseases. However recently, numerous studies have evaluated its use in systemic conditions and in therapeutics where, optic nerve and retinal architecture can be assessed to monitor progression of systemic conditions and its response to treatment. This is a narrative review aimed at evaluating the debate surrounding the role of spectral domain optical coherence tomography, in systemic conditions where optic nerve affection can be measured and be used in the diagnosis, monitoring and assessment of treatment effect as a non-invasive, quick, novel technique.

Keywords: nutrition, optical coherence tomography, retinal nerve fibre layer, systemic disease, therapeutics

Introduction

Optical coherence tomography (OCT) is a technique designed to evaluate *in vivo* qualitative and quantitative changes of the anterior segment, optic nerve and the retina. Since its first use in 1991, with advancing technology, the newer generation spectral domain optical coherence tomography (SD-OCT) has become an integral part of ophthalmic assessment. SD-OCT has faster axial scan velocities, higher axial resolution and better reproducibility than older generation time domain (TD) OCT technology.[1] In recent years, the advent of swept source OCT has allowed better evaluation of diseases affecting the optic nerve head (ONH), as it uses longer wavelengths which allow better penetration.

Initial applications of this technology were confined mainly to ophthalmic diseases. However recently, numerous studies have evaluated its use in systemic conditions and in therapeutics where optic nerve and retinal architecture can be assessed to monitor disease progression and treatment effects. This is a narrative review aimed at evaluating the debate surrounding the role of SD-OCT, in systemic conditions where optic nerve affection can be measured and be used in the diagnosis, monitoring and assessment of treatment effect as a non-invasive, quick, novel technique.

Methods

We included all the relevant published evidence, in English language, on the role of OCT in pathological processes affecting the optic nerve and retina in the following subcategories: neurological disorders; respiratory disorders; autoimmune disease; intracranial trauma; inflammatory conditions; psychiatric disease; nutrition; changes due to medication, malignancy and infectious diseases; and, finally, miscellaneous conditions. This sub-classification was reached after the initial analyses of all the articles published in relation to the topic were retrieved.

A PubMed and Medline search was conducted between 12 August 2016 and 5 July 2017, using

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the following terms within the categories defined above:

1. Neurological disorder

(("Nervous System Diseases"[Mesh]) AND ((((retina or retinal)) AND ("nerve fibre layer" or "nerve fibre layer" or rnfl or "stratum opticum")) AND thickness)) AND "Tomography, Optical Coherence"[Mesh].

2. Malignancy

(malignant or malignancy or cancer or cancers or neoplasm or neoplasms or neoplasia or carcinoma or carcinomas) AND (optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND thickness.

3. Nutritional disorders

((nutrition or nutritional or malnutrition or vitamin or vitamins)) AND ((optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND thickness).

4. Respiratory disorders (COPD, sleep apnoea)

("Respiratory Tract Diseases" [Mesh] AND ((retina or retinal) AND ("nerve fibre layer" or "nerve fibre layer" or rnfl or "stratum opticum") AND thickness)) AND "Tomography, Optical Coherence"[Mesh].

(optical coherence tomography or optical coherence tomographic or OCT) AND (nerve fibre layer or nerve fibre layer or rnfl) AND thickness AND (COPD or chronic obstructive pulmonary disease or emphysema or sleep apnoea or sleep apnoea or sleep disordered breathing).

(optical coherence tomography or optical coherence tomographic or Oct) AND (nerve fibre layer or nerve fibre layer or rnfl) AND thickness AND (bronchitis or bronchial or pulmonary or bronchopulmonary or respiratory or respiration).

5. Psychiatric disorders

("Mental Disorders"[Mesh] or depression or schizophrenia) AND (optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND thickness.

6. Autoimmune disease and Susac syndrome

("Autoimmune Diseases"[Mesh] OR "Susac Syndrome"[Mesh]) AND "Tomography, Optical Coherence"[Mesh] AND ((nerve fibre layer or nerve fibre layer or rnfl) AND thickness).

susac AND ((nerve fibre layer or nerve fibre layer or rnfl) AND thickness).

7. Inflammatory conditions

(vasculitis OR arteritis OR wegner OR wegner's OR polyarteritis OR sarcoid OR sarcoidosis OR takayasu OR churg strauss OR inflammatory) AND (optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND thickness.

8. Infectious diseases

("Bacterial Infections and Mycoses"[Mesh]) OR "Parasitic Diseases"[Mesh]) OR "Virus Diseases"[Mesh]) AND (optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND thickness.

((Infection or infections or infectious or tuberculosis or TB or HIV or human immunodeficiency virus)) AND ((optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND thickness).

9. Miscellaneous

(optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND thickness AND systemic.

10. Therapeutics

(optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND ((((retina or retinal)) AND thickness AND ("Nerve Fibres/drug effects"[Mesh:No

Exp] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR "Steroids/adverse effects"[Mesh] OR "Pharmaceutical Preparations/adverse effects"[Mesh]).

(optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND ((((retina or retinal)) AND thickness) AND (steroids or corticosteroids or steroid or corticosteroid or glucocorticoid or glucocorticoids or ethambutol or vigabatrin or chloroquine or isotretinoin).

The search generated 1997 articles over 15 years (October 2001–July 2016), as shown in Figure 1. Articles that were not in English were excluded. The articles were then manually reviewed to exclude those relating primarily to ocular disease (such as macular degeneration), paediatric cases and studies in healthy subjects. We also excluded articles on the SD-OCT use in systemic diseases with widespread retinal complications such as vascular conditions like diabetic retinopathy and hypertensive retinopathy, as these were not the aim of this review. Thereafter, the articles were further evaluated to include studies, which used fourth-generation SD-OCT. These articles were then categorised according to the level of evidence as per the Scottish Intercollegiate Guidelines Network (SIGN) classification. For the purpose of this review, evidence from meta-analyses, systematic reviews, randomised controlled trials, case control and cohort studies was included. Non-analytical studies such as case reports or case series were included only if there were two or more articles with supporting evidence in order to incorporate rare diseases as an indicator of future areas of research. We excluded articles reflecting expert opinion and letters to the editor.

Review of diseases

Neurology
Idiopathic intracranial hypertension. Idiopathic intracranial hypertension (IIH) is a disorder of raised intracranial pressure (ICP) that mainly affects overweight women of childbearing age.[2,3] The natural history of the disease is variable. Some degree of vision loss occurs in 86% of patients, and 10% can develop severe visual symptoms.[3] Early diagnosis, appropriate treatment and careful follow-up with combined assessment of optic disc morphology and visual field (VF) are vital for preserving vision. In practice, Frisen[4] scale has been the standard method for evaluating papilloedema and monitoring the alterations in the ONH. It is a non-continuous ordinal grading based on descriptive features described in fundus photographs or on ophthalmoscopy.[4] However, although the scale is useful clinically, it lacks sensitivity to small changes in the degree of disc oedema, and grading can vary among observers.[5,6] Determining progression or regression can be obscured by ischaemia, gliosis and dilated venules.[5,6] In contrast, SD-OCT with three-dimensional (3D) segmentation of the retinal nerve fibre layer (RNFL), provides reliable, reproducible measurements that reflect the effects of intracellular and extracellular oedema and axonal loss and thinning.[5,7,8] These measurements can give a continuous quantitative assessment of papilloedema that correlates with Frisen grading and are an objective indication of disease severity.[5,7,8] The additional advantage of measuring several parameters such as alterations in the ONH and total retinal thickness (TRT) and retinal ganglion cell layer (RGL) allows for in-depth interpretation of changes. This is aided by 3D segmentation of SD-OCT images.[9] Severe papilloedema and multiple disc haemorrhages can make it difficult to ascertain the posterior border of the RNFL with the OCT due to technical challenges, and in such situations, it has been hypothesised that TRT may be useful and superior to RNFL thickness alone.[5,10] However, this needs further research and evolving technology to improve OCT-based algorithms to assess severe papilloedema.[5,9,10]

Quantification of optic disc changes related to resolution of papilloedema during regulated medical therapy is also possible with SD-OCT. The papilloedema outcomes from the OCT sub study of the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) showed that OCT assessments of papilloedema improved after weight loss with or without acetazolamide therapy.[11] This was supported by the findings of Skau and colleagues,[10] where 1.5 g/day of acetazolamide tended to normalise OCT within 2–3 months and lead to symptomatic relief in 94% of patients. In this study, improvement in OCT was accompanied by corresponding improvement in VF mean deviation.

It is important to bear in mind that OCT and automated perimetry offer different but complimentary physiological and anatomical information and therefore are best used in combination to monitor IIH patients.
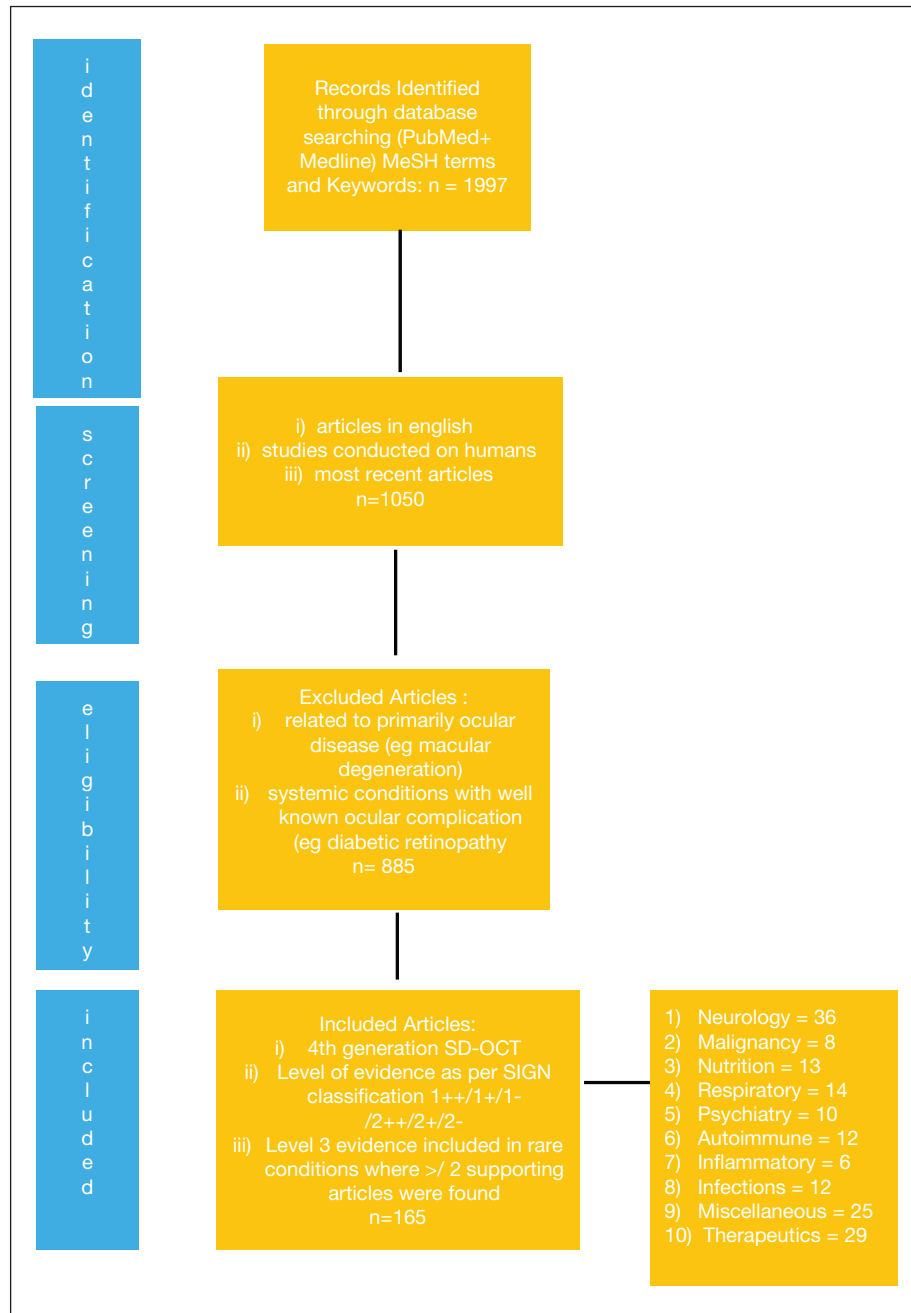
Figure 1. Flow diagram of search steps.

In conclusion, 3D segmentation of SD-OCT can be used in grading mild to moderate papilloedema. More research is needed to evaluate the role of OCT in assessing severe papilloedema, where current OCT programmes pose technical challenges. Response to treatment can be quantified using OCT to measure RNFL and ONH thickness and when used in conjunction with VFs can be useful in monitoring patients' response to treatment.

Multiple sclerosis. Multiple sclerosis (MS) is a common neurological disease, characterised by recurrent inflammatory episodes within the central nervous system (CNS), causing demyelination, axonal loss and neuronal degeneration, leading to permanent functional disability. Interestingly, within the eye, the RNFL consists of axons that are unmyelinated, with myelination starting after the optic nerve. This is a unique advantage, whereby RNFL consists of easily

visible neurones which makes it an ideal structure for studying the process of neurodegeneration and neurorepair.[12]

Parisi and colleagues[13] reported the earliest application of OCT in MS. The study revealed that RNFL thickness was not only reduced in MS patients who suffered an acute episode of optic neuritis (ON) but also in 'unaffected' eyes although not to the same extent. Further longitudinal studies have confirmed this finding, indicating that a more subtle RNFL loss can occur in MS due to presumed retrograde trans-synaptic retinal ganglion cell (RGC) degeneration.[14–17]

Progressive thinning of the RNFL can start early in MS with or without a prior history of ON, and the maximal loss was seen in the papillomacular bundle in all MS subtypes, and this can be reduced by 10–60% of normal, depending on disease severity, duration and history of ON.[18,19] It is now recognised that macular volume is also reduced in MS. Approximately, 34% of the macular volume is made up of ganglion cells and their axons, so it may be expected that macular volume loss would follow RNFL loss.[20] However, OCT evidence of macular thinning has recently been demonstrated even in the absence of RNFL thinning. There is also evidence of damage to retinal layers with inner and outer retinal atrophy in the macular area.[21] Reduction in macular volume is characteristic in relapsing-remitting multiple sclerosis (RRMS) and can be found at baseline in many patients within this subtype.[22]

Most MS patients present with an RRMS that may transform into secondary progressive multiple sclerosis (SPMS), whereas a smaller percentage of patients present with primary progressive multiple sclerosis (PPMS) from the start.[23]

Currently, there is extensive research in evaluating RNFL and macula thickness in MS subtypes. Although this has shown that between subtypes, overall RNFL values and predominantly the temporal quadrant thickness are significantly reduced in SPMS patients compared with RRMS,[24] there is no consistent evidence at present; some have shown good correlation[25] while others have failed to achieve statistical significance.[26,27] However, results suggest that retinal axonal damage can occur without clinical ON as a part of MS progression, and OCT can be used as a potential biomarker.

Retinal architecture has also been shown to correlate with visual function. Costello and colleagues[25] identified an injury threshold where overall RNFL thickness below the threshold level led to a corresponding decline in automated perimetry. A similar relationship was seen between RNFL decline and low contrast letter acuity.[28] Both amplitude and latency of visual evoked potentials (VEPs) have been shown to deteriorate with corresponding decline in RNFL thickness.[29,30] Fisher and colleagues[28] quantified this functional decline by measuring increasing neurological impairment as evaluated by the expanded disability status scale and showed that it is directly proportional to the average overall RNFL thickness.

There is also a good correlation between RNFL thickness and brain atrophy, evaluated using magnetic resonance imaging (MRI).[31–33] Interestingly, Grazioli and colleagues[32] found that RNFL thickness in MS non-ON patients was associated with a reduction of brain parenchyma fraction and percentage grey matter. A similar association was not present in MS patients with ON. The authors pointed out that axonal loss after ON occurs independently of brain atrophy, whereas in non-ON cases, RNFL degeneration was associated with the degenerative process in the brain.

In summary, the application of OCT as a biomarker of MS is vast. First, there is a clear pathological correlation with axonal loss. Second, the analytical reproducibility is excellent, and finally, OCT is of high clinical relevance, correlating with clinical measures such as visual function and disability.

Neuromyelitis optica. Neuromyelitis optica (NMO) is an autoimmune condition, which causes simultaneous inflammation and demyelination of the optic nerve and spinal cord. It is known to have a remitting relapsing course similar to MS; however, in NMO, a specific immune target, namely the aquaporin 4 on the surface of astrocytes has been identified. No specific immune target has yet been identified in MS. OCT has rapidly gained importance as a tool to quantify optic nerve damage in this condition. Greater loss of RNFL and subclinical damage are notable features of NMO.[34–37] This can cause significant reduction in visual acuity and field, when compared with MS patients.[34,38]

Recently, Monteiro and colleagues[34] compared structure–function differences between MS and NMO with and without history of ON and found that the two conditions differed significantly in their relationship between retinal axonal loss and VF defect. It was noted in patients without prior history of ON the correlation between RNFL thickness and corresponding VF defects was stronger in NMO due to greater axonal loss. However, the correlation between VF defect and macular thickness was greater in MS patients, where loss of macular thickness can be independent of RGC loss and can be accounted by atrophy of other retinal layers. This has highlighted differences in retinal pathology between the two diseases in the absence of ON. Thus, it has been suggested that OCT features along with brain and spinal cord MRI can help differentiate MS from NMO.

Alzheimer's disease. Alzheimer's disease (AD) is a neurodegenerative disease, which often starts as a mild cognitive impairment (MCI).[39] It is difficult to diagnose especially in its early stages due to the lack of physical and neurological findings that are specific to the disease. RNFL thinning may be the earliest finding of AD: even before memory impairment,[40] OCT data from meta-analyses have shown a significant decline in RNFL thickness in all four quadrants of the retina as well as reduced macular volume in AD and MCI patients than age-matched controls, suggesting that the pathology affects the entire retinal layer and cannot be attributed to ageing alone.[41] A reduction in RNFL thickness has been shown to be directly proportional to abnormalities in pattern electroretinogram (pERG), suggesting that neuronal degeneration occurs in the RGL.[42,43] However, these were not related to changes in cortical VEP and therefore unlikely to be a result of retrograde degeneration.[44]

Clinical correlation between reduction of total macular volume and the degree of cognitive impairment as assessed by the Mini-Mental State Examination (MMSE) have produced positive results.[45,46] They have also produced negative results.[47–50]

These findings suggest that RNFL thickness can be used to distinguish AD patients from normal ageing. Moreover, OCT can be useful to detect early RNFL abnormalities in MCI patients. However, its role as a measure of disease severity and an aid to identifying MCI patients with higher predisposition to convert to AD remains to be determined.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary small-vessel disease caused by Notch3 mutations.[51] Histologically, it is characterised by accumulation of granular osmiophillic material in systemic, specifically intracranial, vasculature.[52] Clinically, it manifests as migraines, transient ischemic attacks and strokes leading to dementia and physical and visual disabilities.[53–56] The wide spectrum of signs and symptoms and the technical challenge of examining brain micro vessels *in vivo* make diagnosis difficult. Although MRI findings show characteristic white matter subcortical involvement particularly in the anterior temporal lobe and internal capsule in early stages of the disease, they are by no means specific to CADASIL.[57] *In vivo* imaging of retinal vessels SD-OCT is evolving as a new diagnostic approach. Alten and colleagues[58] reported the first study exploring retinal findings and retinal vessel measurements in CADASIL patients using high-resolution SD-OCT. They found that the RNFL was thicker globally and hypothesised that this may be caused by pathological enlargement of retinal vessel diameter which runs through the RNFL. They also visualised and measured increased retinal venous lumina, thickened vessel walls and reduced arterial lumina representing ischaemia. In the future, retinal imaging may be used as a complementary tool along with MRI, genetic diagnostics and immunohistology, to diagnose and follow-up CADASIL patients and other cerebral small-vessel diseases.

Parkinson's disease. Parkinson's disease (PD) is a commonly encountered neurodegenerative disease among the ageing population. The accuracy of clinical diagnosis is limited especially in early stages when signs are inconclusive and neuroimaging fails to provide characteristic features.[59] OCT data from meta-analyses have shown a reduction in average circumpapillary RNFL thickness comparing PD to age-matched controls specifically in the temporal quadrant.[60] This may be due to a greater susceptibility of the temporal fibres to neurodegeneration or as a result of involvement of the papillomacular bundle. The pathophysiology of retinal thinning is believed to be due depletion of dopaminergic

amacrine cells, which is a well-known consequence of PD. Retinal dopamine (DA) deficiency can alter visual processing by modifying ganglion cells.[60] It has been hypothesised that diminished dopaminergic input to ganglion cells can lead to atrophy.[61] OCT data from several studies have confirmed these findings, where mean peripapillary RNFL thickness as well as the total macular volume have been reduced in patients with PD.[62,63]

Visual hallucinations (VH) are a specific feature similar to Charles Bonnet syndrome and thought to be a result of deteriorating visual acuity, contrast sensitivity and defective visual information processing from both the central and peripheral pathways, as the disease progresses.[64] RNFL thinning in PD has been reported to be strongly associated with VHs and correlated with PD duration and severity.[63] Thus, it is possible that the thinning of the retinal layers can be an indication of disease progression and risk of VHs in PD.[63]

In view of these results, OCT could be a useful tool for evaluating structural changes in the early diagnosis and progression of the neurodegenerative disorders such as PD.

Chiasmal compression. Pathologies causing compression of the chiasm can lead to loss of visual acuity, colour vision as well as VF defects. Although surgical excision helps with visual recovery, this recovery can be variable and unpredictable.[65–67] Traditionally, these conditions have been diagnosed and monitored by neuroimaging and VFs; however, recent studies have shown that RNFL and RGC thinning as measured by OCT, correlate closely with VF loss[68,69] and can also be used to detect early changes before VF loss occurs.[68,69] Tieger and colleagues[69] found that binasal RGC loss could be seen in patients with compression with minimal (or before detectable) VF loss and before RNFL was affected. Patients with less RGC loss had better visual recovery postoperatively. Reversibility of visual dysfunction has also been shown to be related to the loss of RNFL thickness. In patients with normal RNFL thickness, visual function shows large improvements in the presence of advanced preoperative VF or acuity loss, whereas patients with thin RNFL and advanced VF defect demonstrate significantly less improvement.[70,71] Loo and colleagues[72] specifically demonstrated that RNFL thickness below an injury threshold pre

dicts a lesser probability of visual improvement after decompression surgery or radiation therapy for anterior pathway meningiomas and thus may be useful in predicting posttreatment visual recovery. Unlike other modalities, which cannot differentiate between reversible and irreversible factors, OCT can quantitatively measure axons by measuring RNFL and RGC thickness and can therefore be used to monitor and provide a prognostic indicator in chiasmal compression. However, it is important to note that OCT cannot distinguish normal density from swollen but reduced cell density so these results need to be interpreted with caution.

Haematological malignancy

RNFL loss in patients with haematological malignancy can lead to VFs defects.[73] The pathophysiology may be chronic vascular insufficiency, chronic ischaemic injury due to anaemia or damage from retinal haemorrhages, which can be a result of platelet count changes.[74–76] Han and colleagues[73] found patients with haematological malignancies had reduced RNFL thickness in the 11 o'clock sector of the optic nerve compared with healthy controls, and reduction was proportional to the severity of anaemia. The authors found lower haemoglobin (Hb) levels were associated with RNFL thinning and RGC loss. Further studies are required to evaluate whether these defects and VF defects are progressive and whether treatment can reverse changes or prevent progression.

Nutrition

Vitamin B12 deficiency. Vitamin B12 deficiency is a common nutritional disorder associated with megaloblastic anaemia, gastrointestinal disorders and neuropsychiatric disorders as well disorders of the visual pathways.[77–79] The neurological pathophysiology starts with demyelination followed by axonal degeneration and irreversible cell damage.[80] Increasing knowledge and awareness of this at an early stage enable detection and treatment with supplements. Diagnosis can be difficult in patients with subclinical vitamin B12 deficiency without anaemia. However, if treatment is delayed in these patients, there may be permanent neurological sequelae. In all patients with unexplained neuropsychiatric symptoms, vitamin B12 deficiency should be suspected. OCT can be used to obtain cross-sectional images of the peripapillary RNFL, as this has been shown

to be decreased especially in the temporal quadrant with involvement of the papillomacular bundle.[79,81,82] This reduction has been attributed to a decrease in myelinisation, since vitamin B12 is a major co-factor in the synthesis of myelin. Interestingly, thinning of the RNFL can be seen before patients have manifest VF defects.[81] Therefore, OCT can be used to detect early subclinical structural changes.

Vitamin D deficiency. Traditionally, vitamin D is known to play an important role in bone formation and mineral homeostasis. Recent studies have shown that it can affect immune and CNS development and function and has immune regulatory capacity.[83,84] There is accumulating evidence that vitamin D has a protective role in the development and progression in various systemic conditions that affect the nervous system. Evaluation of the retinal architecture with OCT scans in patients with vitamin D deficiency has shown reduced macular thickness specifically the macular ganglion cell layer (GCL).[85,86] Uro and colleagues[86] also demonstrated that in patients with early vitamin D deficiency, thickness of the GCL was reduced without affecting the RNFL. Additional thinning of the RNFL occurred at a later stage. Thus, these findings indicate that OCT may be used to detect subclinical changes in vitamin D deficiency and may also have a role in monitoring progression. Further studies are required to evaluate whether these defects are reversible with treatment and whether OCT can be used as a quantitative measure.

Respiratory disorders

Obstructive sleep apnoea hypopnea syndrome. This is a condition characterised by brief episodes of partial or complete obstruction of the upper airway during sleep with resultant hypoxia.[87]

Different ophthalmological conditions have been associated with this condition including optic neuropathy as well as a presumed increased incidence of glaucoma.[87]

OCT as a non-invasive, reproducible, imaging technique has been used to study RNFL, ONH, macular thickness and volume to assist in diagnosis and monitor progression.

Several studies evaluating OCT assessment of the peripapillary RNFL in patients with obstructive sleep apnoea hypopnea syndrome (OSAHS) have reported thinning of this layer, nevertheless age-related thinning of this layer and increased incidence of glaucoma in these patients implies cautious interpretation of these findings.

Sun and colleagues[88] and Zhao and colleagues[89] suggested that OSAHS patients tend to have thinner RNFL. The overall mean difference was higher in moderate and severe OSAHS cases as indicated by the Apnoea Hypopnoea Index (AHI). Mild cases did not show significant difference from healthy controls. The inferior quadrant of the RNFL followed by the superior quadrant were reported to suffer the most; however, the temporal quadrant may to be spared and some studies have reported increased thickness secondary to hypoxia which can cause raised ICP with secondary swelling of the optic nerve.[90]

Although the correlation between the severity of the condition and the degree of thinning was not universal,[91] a recent meta-analysis by Wang and colleagues[60] showed the pooled weighted mean difference (WMD) for the average RNFL thickness and any of the quadrants was significantly lower in patients with OSAHS, compared with healthy subjects, and this difference increased with increasing severity of the condition.

In summary, OCT of the RNFL can be a useful ancillary test to monitor and assess severity of the condition; however, further longitudinal studies are required to establish specific changes.

Psychiatry

Schizophrenia. In spite of the lack of characteristic neuropathological abnormalities in schozophrenia, the neurodegenerative nature of this condition has been confirmed by MRI and neuropathological studies.[92] Reduction in grey matter volume and decreased size and density of neurons in the hippocampus and thalamic area have been demonstrated.[92]

In vivo imaging of the unmyelinated retinal nerve fibres by OCT provides an opportunity to study neurodegenerative disorders of the CNS.[93]

Studies, which investigated the use of OCT to measure different retinal parameters in schizophrenic patients, reported heterogeneous results.[5,94] Some reported overall reduction of the RNFL thickness, others showed reduction of

specific quadrants,[5,94] whereas others have failed to show any co-relation at all.[93]

Lee and colleagues[95] showed significant reduction of the overall thickness of the peripapillary RNFL in schizophrenic patients with macular thinning and macular volume loss, which were more prominent in patients with chronic disease.

Yılmaz and colleagues[96] and Celik and colleagues[97] reported that the volume of the GCL and the internal plexiform layer is also reduced in these patients. Furthermore changes in these two layers are strongly related to the severity of the disease more so than changes in the RNFL.

Although the existing evidence does not allow for a definite evaluation for the role of OCT as a biomarker in schizophrenia, it confirms the neurodegenerative nature of the disease, and future research is needed to define the extent of correlation between changes in retinal parameters and the disease severity and duration as well assessing the sensitivity and specificity of the test.

Major depression and bipolar disorder. Major depression is a chronic or recurrent mood disorder with underlying neurodegenerative processes affecting certain areas of the cerebral cortex as confirmed by neuroimaging studies, postmortem and animal studies. Schönfeldt-Lecuona and colleagues[98] suggested that OCT may be used as a diagnostic tool to evaluate the neurodegenerative process in psychiatric disorders including depression. In their study, RNFL thickness in patients with major depression did not differ from healthy controls, but a negative correlation was noticed between the duration of the latest depressive episode and the thickness of the ganglion cell inner plexiform layer (GCL) and nasal RNFL. Yıldiz and colleagues[99] found the total RNFL thickness to be positively correlated with the quick inventory of depressive symptomatology (QIPDS) score. However, the small sample size and the mild symptoms in the study patients imply cautious interpretation of the results. Thinning of the RNFL has also been reported in patients with bipolar disorder. Mehraban and colleagues[100] found thinning of RNFL on OCT in all quadrants except the temporal quadrant when compared with healthy controls, and the extent of thinning was significantly correlated to the duration of the illness. However, in these studies, although the controls were age and sex matched, body mass index (BMI) was not considered. BMI and nutrition status is an important contributing factor in RNFL thickness and overall functioning of the visual pathway. This is significant in studying a population with major depression or bipolar disorder, as these patients often suffer from nutritional deficiencies due to self neglect. Quantifying OCT parameters as an indicator of neurodegeneration in patients with psychiatric disorders need further evaluation with larger studies, which accounts for nutritional status, BMI and the toxic effects of smoking and other recreational drugs on RNFL thickness.

Anorexia nervosa. Anorexia nervosa (AN) is a multisystem disease. Ocular effects may involve corneal ulceration, cataracts, rod dysfunction and vein occlusion. Moschos and colleagues[101] reported that patients with this disorder and normal vision have a statistically significant lower overall RNFL and foveal thickness as well as altered electrical activity of the macula when compared with normal controls. The multifocal ERG patterns of these patients go against nutritional deficiencies such as vitamin A deficiency, so the authors have hypothesised that the changes may be related to impairment of dopaminergic neurotransmission as a result of food restriction or related to the underlying pathophysiology of AN. DA is an important neurotransmitter in the visual pathway and reduced dopaminergic input can cause atrophy of selected optic nerve fibres. These findings were also found to be related to BMI at presentation and duration of disease, RNFL thickness being negatively correlated to both.[102] In addition, patients with different subtypes of AN, namely restrictive AN and purge type AN, exhibited differences in overall retinal thickness of the macula, values being higher in the restrictive type which indicates that the anatomical impairment of the fovea maybe greater in the purge type AN. These findings suggest that OCT can help us understand the pathophysiology and ocular effects of AN, a subject that is currently poorly understood.

Inflammatory and autoimmune disorders
Rheumatoid arthritis. SD-OCT has been used to study the choroid, foveal thickness and RNFL in patients with rheumatoid arthritis (RA). Tetikoglu and colleagues[103] reported that the mean sub foveal, nasal and temporal choroidal thickness was significantly higher in patients with RA. However, RNFL and foveal thickness did not show significant difference in RA patients when compared

with healthy controls.[103] On the contrary, Duru and colleagues[104] reported lower mean sub-foveal choroidal thickness as well as thinner para-foveal choroid in patients with RA. No correlation was seen between the choroidal thickness and disease activity as measured by Disease Activity Score-28 (DAS-28).[104]

The contradictory results of these studies may be explained by the difference in sample size and the heterogeneity of the study sample with regard to disease activity. However, it is interesting to note both pointed to changes in the choroidal layer as part of the systemic vasculature. These changes were also shown to vary with the disease activity. Further studies evaluating OCT assessments in such patients could help us understand the disease process and its implications better.

Systemic lupus erythematosus. SD-OCT has been used to assess macular thickness and RNFL in patients with this multisystem autoimmune disorder. It was reported that the mean sub foveal, nasal and temporal choroidal thickness was lower in these patients.[105] Although RNFL thickness was reported to be lower in patients with systemic lupus erythematosus (SLE), the presence of neuropsychiatric complications did not correlate with the degree of RNFL loss.[106] It was also noted that the loss of the temporal RNFL was positively correlated to cognitive function.[106] This raises the possibility that OCT measurement of the macular thickness and RNFL can be a useful marker for early involvement of the retina and the CNS in patients with SLE.

Autoimmune retinopathy. This involves a spectrum of rare but visually devastating immune-mediated retinal degenerations characterised by acute or subacute visual loss, abnormal ERG and the presence of antibodies to retinal antigens. Autoimmune retinopathy (AR) includes carcinoma-associated retinopathy (CAR), melanoma-associated retinopathy (MAR) and non-paraneoplastic-associated retinopathy (NPAR). The role of OCT in this condition was clearly highlighted in two retrospective case series by Abazari and colleagues[107] and Pepple and colleagues.[108] In addition to establishing the diagnosis in patients with unexplained visual loss, OCT can give an insight into the cause of this and help in monitoring as well as assessing the response to treatment.

Both studies showed that the damage is mainly targeting the outer retinal complex, namely the ellipsoid zone (EZ), external limiting membrane (ELM) and outer nuclear layer (ONL). The RNFL and GCL were reported to be spared in these two studies with reduced foveal and central macular thickness being noticed as well.

Nevertheless, Sepah and colleagues[109] with SD-OCT confirmed that the loss involves all retinal layers including the RNFL and GCL.

Behcet disease. Both peripapillary RNFL and macular thickness were reported to be lower in patients with neuro-Behcet than in healthy age-matched controls, and the temporal quadrant of the RNFL seems to be spared.[110] Furthermore, localised defects in the RNFL not associated with scarring were detected on OCT examination, and these may give an indication of posterior segment involvement in Behcet disease (BD), which carries poor visual prognosis.[111] The use of enhanced depth imaging (EDI)-OCT to study choroidal thickness in both the active and quiescent phase of the disease showed higher thickness in the active phase and was greater in patients with BD than healthy controls.[112]

Susac syndrome. This is an autoimmune microvasculopathy with predilection to the brain, retina and inner ear, the most challenging differential diagnosis being MS.

Brandt and colleagues'[113] cross-sectional multicentre observational study reported that patients with Susac Syndrome (SS) have lower RNFL thickness and macular measurements than healthy controls and patients with RRMS irrespective of a history of ON. The majority of patients with SS showed a distinct severe and patchy thinning of the RNFL, which was also reported by Bernard and colleagues.[114] The loss was more on the nasal quadrant with an abnormal foveal contour, and the extent and degree of OCT abnormalities were correlated with the stage and severity of the disease. Apart from the RNFL, other layers namely GCL, inner plexiform, inner nuclear and outer plexiform were reported to be thinner in patients with SS as well. However, the ONL and the retinal pigment epithelium are not affected suggesting retinal rather than choroidal damage.[115]

OCT clearly has a distinct pattern in patients with SS which can help to differentiate this condition from RRMS even in the absence of the characteristic branch retinal artery occlusion (BRAO) and

can be used as a non-invasive tool to monitor patients with BRAO instead of fluorescein angiography.

Infectious diseases

HIV and AIDS syndrome. Since its discovery in the early 1980s, HIV has presented itself as a constant challenge for healthcare professionals worldwide with regards to management of the long-term health effects in people living with HIV. Thankfully, the introduction of highly active antiretroviral therapy (HAART) was the stepping stone in improving the long-term outlook in terms of morbidity and mortality in this patient group.[116] The incidence of opportunistic infections has significantly been reduced since the further development and better patient access to HAART. However, a new spectrum is emerging in the form of metabolic and neurologic degenerative phenomena, which may have a long-term impact on the ageing process. The term HIV-associated 'neuroretinal disorder' has been described in the literature but remains poorly understood.[117]

It appears that the maculae of HIV-infected individuals tended to be thicker than age- and gender-matched HIV negative individuals. This could be explained by inner retinal oedema secondary to HIV-related retino-vascular disease.[118]

On quantification of the periapapillary RNFL thickness of the four quadrants, there was a direct relationship between RNFL thickness and duration of HIV treatment. It was found that the longer the patients were on HAART, the more likely they were to have thinner RNFLs, especially in the inferior and nasal quadrants.[119]

In addition, HIV patients who had low CD4 counts (<100 cells/mm^3 for at least 6 months) had significantly thinner average RNFLs than patients who had healthier CD4 counts (>100 cells/mm^3) since diagnosis.[120]

In conclusion, OCT may be useful to diagnose early subclinical HIV-associated visual functional loss, with more prospective, larger-scale research needed to analyse the various correlations noted above.

Therapeutics

Vigabatrin. Damage to vision from vigabatrin toxicity is an important safety concern.[121,122] Currently, both VF testing and electroretinography are used to monitor patients.[123,124] Vigabatrin-attributed field loss can exist in the presence of an apparently normal ONH and retina or can be associated with ONH pallor with or without a variety of accompanying subtle retinal abnormalities. These abnormalities include surface wrinkling retinopathy, peripheral retinal arterial narrowing, abnormal pigmentation and thinning of either the peripapillary or peripheral RNFL.[125] OCT can be used to provide a more objective means of assessing retinal damage. Studies have shown that in vigabatrin toxicity, peripapillary RNFL thinning occurs first in the nasal quadrant with sparing of the temporal retina with or without involvement of the superior and inferior retina.[126–128] Peripapillary nasal RNFL thinning can be one of the earliest signs of toxicity even before VF loss and has been seen in patients receiving cumulative doses of 1000 g or less in the presence of normal VFs.[129] The time to occurrence of an attenuated RNFL thickness resulting from vigabatrin therapy is unknown, neither is the extent of any further attenuation over time.[125] However, with higher cumulative doses of vigabatrin exposure, additional RNFL thinning can occur which is proportional to VF loss.[129] Vigabatrin is often used as an adjunctive anti-epileptic medication for partial onset epilepsy, which is not satisfactorily controlled by conventional therapy, and as monotherapy for infantile spasm, particularly secondary to tuberous sclerosis.[129]

Unfortunately children on vigabatrin often are not able to cooperate with VF or ERG testing and often require general anaesthesia for drug monitoring. Given these challenges, OCT may be an option for patients who can tolerate imaging while awake or perhaps decrease anaesthesia time. In conclusion, OCT can be a useful diagnostic tool and serves as an adjunct to VF testing or can even be used in isolation for patients who do not tolerate other forms of assessments in monitoring vigabatrin-induced retinal toxicity. However, the C pattern or 'inverse atrophy' often seen in these cases can be confounded by the presence optic nerve hypoplasia and other coexisting pathologies, and OCT findings need to be interpreted in caution when used alone.[130]

Antituberculous medication. Antituberculous medication, especially isoniazid and ethambutol commonly cause drug-related optic neuropathy.[131] Prediction of onset and consequent drug withdrawal is essential to stop visual loss. OCT evaluation of peripapillary RNFL thickness has

shown significant reduction in all quadrants with maximal involvement in the temporal quadrant and with marked involvement of the papillomacular bundle.[131–133] These changes have also been seen in patients on isoniazid.[134] Furthermore, structural change has been shown to correlate well with severity of visual impairment and visual recovery after discontinuation of treatment where patients with thicker papillomacular bundles have a better prognosis.[132] Wei and colleagues[135] also demonstrated that ethambutol toxicity could specifically cause reduction of macular thickness. In this study, reduction in macular thickness was proportional to reduction in visual sensitivity and the authors suggested that macular thickness maybe the optimal structural marker to detect early ethambutol toxicity. Thus the OCT can be used as an objective measure of detecting early structural damage in ethambutol toxicity as well as help predict visual recovery on cessation of the drug.

Chloroquine and hydroxychloroquine. The antimalarial drugs, chloroquine (CQ) and hydroxychloroquine (HCQ) have been used in the treatment of various rheumatologic diseases such as RA, SLE and other inflammatory and dermatological conditions. Retinal toxicity is a serious complication of both drugs and appears to be dose related, with HCQ being considered a safer option.[136] The effects may be reversible on discontinuation of the drug at the preclinical stage if changes are detected early.[137,138] In the preclinical stage, patients may be asymptomatic, and the fundus may remain normal with no detectable of maculopathy.[138] Hence, screening for early detection in the preclinical maculopathy stage is recommended.[138,139] Screening can be challenging due to lack of fundal findings at early stages and variability of functional tests. Recent studies have shown that changes in retinal thickness and loss of inner retinal layers can be detected by SD-OCT in patients with early CQ and HCQ toxicity, even in areas that appeared normal on fundoscopy and perimetry.[140–142] Patients exhibit thinning of the foveal and parafoveal areas in early stages and thinning of the inner retinal layers at the posterior pole can be seen before the appearance of retinal lesion and peripapillary RNFL thinning.[142] Given the toxic nature of both drugs and of CQ in particular, SD-OCT could be a helpful screening tool for the detection of preclinical macular toxicity in conjunction with other functional tests (such as VF perimetry) early in the course of CQ treatment.

Chemotherapy. The use of chemotherapeutic agents can induce adverse side effects in the eye.[143] Bakbak and colleagues[144] looked at the effects of cisplatin and paclitaxel on RNFL, two chemotherapeutic agents that are known to cause neurotoxicity.[145–147] The study demonstrated a reduction in the peripapillary RNFL thickness and correlated with VF defects on frequency-doubled perimetry, indicating that these agents damage the RGC axons.

Moschos and colleagues[148] evaluated the effects of aromatase inhibitors (AIs) used in patients with breast cancer on peripapillary RNFL thickness, optic nerve and macular function. The study showed that AIs significantly decreased RNFL thickness (overall average, superior and inferior). Structural changes correlated with functional tests with evident decrease on visual acuity and delayed VEPs (both amplitude and latency of P100).

Although there may be difficulties in differentiating drug-related changes on the retina from effects of the malignancy itself, given the widespread systemic effects of these disease processes, OCT could potentially be an essential adjunct to functional tests such as visual acuity and perimetry in screening for the ocular toxicity of these agents.

Conclusion

Systemic disease affecting the choroid, retinal layers and optic nerve are better understood and evaluated due to the advent of high definition OCT imaging.

The technology uses low-coherence interferometry to generate images. A low-coherence near-infrared light beam is directed towards the target tissue, and the magnitude and relative location of the backscattered light from the different layers of the tissue are interpreted by the OCT to generate an image.[149] Staurenghi and colleagues[150] have developed a nomenclature consensus for the classification of the retinal and choroidal layers. The innermost retinal layers identified by OCT are the RNFL, which corresponds to the axons of the ganglion cell and, the ganglion cell inner plexiform layer composed of ganglion cell bodies.[150] Although they represent parts of the same cell, the measurement of their thicknesses is taken at different locations by OCT. The GCL thickness is measured at the macula, where the

concentration of cell bodies is higher, whereas the RNFL thickness is measured at the centre of the optic disc.[151] Scan position can often affect the readings of the RNFL, and in such instances, it is important to interpret these readings in context of the GCL measurements, as these are not influenced by positioning of the scanning diameter.[151] Unfortunately, GCL measurements are not available in all OCT machines; however, new generation machines are looking to integrate of all these parameters.

The inner retinal layers are a key marker in neurodegeneration and retinal vascular pathology. The outer retinal layers are often affected in isolation as is seen in AR or, secondary to choroidal disease and extensive damage to inner retinal layers.

The measurements of these different layers are normally stored within the OCT system, which are then available for analysis using different protocols designed for different applications.[149] In most studies considered in this review, integrated custom analysis was used which gives an overall gross estimate of the measurements taken. Manual segmentation of the layers can help eliminate inaccuracies, which can be dependent on scan position and misaligned signals in unhealthy tissue.[152] Many researchers are now focusing on segmentation of retina in OCT images to produce the retinal thickness maps and to find a correlation between the quantitative and morphological features of the map and different retinopathies.[153]

The implications of this evolving imaging technique in non-ophthalmic disease are widespread. Knowledge of the pathophysiology of these conditions and the ability to interpret OCT findings is fast becoming essential for both ophthalmologists and non-ophthalmic clinicians. There is opportunity for further research in this area as well as collaborative work. There are many challenges to overcome before SD-OCT becomes part of the routine diagnostic tests. This review highlights its use as an adjunct to other modalities in diagnosing and monitoring systemic conditions and its response to treatment.

At present, there are still a lot of variations in the measurements of the different parameters, such that the changes seem rather ubiquitous and may become of limited value. This may be refined further when combining structural assessment with functional assessment (such as visual acuity or VF perimetry). With more OCT machines looking to incorporate structural and functional assessment in one device and to combine this in smaller, portable devices, the future incorporation of this technology in a variety of clinical settings is likely to open numerous new frontiers.

From a proactive and practical perspective, the immediate action, that may be both possible and beneficial, is for physicians of different levels of experience to consider training in the interpretation of OCT images, since its use is now becoming common practice.

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Appendix 1

Literature review search strategy
Database used:

- PubMed search;
- Medline.

Timeline:
From 1 October 2001 to 31 July 2016 = 15 years
Search Strategy

1. (("Nervous System Diseases"[Mesh]) AND (((((retina or retinal)) AND ("nerve fibre layer" or "nerve fibre layer" or rnfl or "stratum opticum")) AND thickness)) AND "Tomography, Optical Coherence"[Mesh].
2. (malignant or malignancy or cancer or cancers or neoplasm or neoplasms or neoplasia or carcinoma or carcinomas) AND (optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND thickness.
3. ((nutrition or nutritional or malnutrition or vitamin or vitamins)) AND ((optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND thickness).
4. ("Respiratory Tract Diseases"[Mesh] AND ((retina or retinal) AND ("nerve fibre layer" or "nerve fibre layer" or rnfl or "stratum opticum") AND thickness)) AND "Tomography, Optical Coherence"[Mesh].

(optical coherence tomography or optical coherence tomographic or OCT) AND (nerve fibre layer or nerve fibre layer or rnfl) AND thickness AND (COPD or chronic obstructive pulmonary disease or emphysema or sleep apnoea or sleep apnoea or sleep disordered breathing).

(optical coherence tomography or optical coherence tomographic or Oct) AND (nerve fibre layer or nerve fibre layer or rnfl) AND thickness AND (bronchitis or bronchial or pulmonary or bronchopulmonary or respiratory or respiration).

5. ("Mental Disorders"[Mesh] or depression or schizophrenia) AND (optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND thickness.
6. ("Autoimmune Diseases"[Mesh] OR "Susac Syndrome"[Mesh]) AND "Tomography, Optical Coherence"[Mesh] AND ((nerve fibre layer or nerve fibre layer or rnfl) AND thickness).

susac AND ((nerve fibre layer or nerve fibre layer or rnfl) AND thickness)

7. (vasculitis OR arteritis OR wegner OR wegner's OR polyarteritis OR sarcoid OR sarcoidosis OR takayasu OR churg strauss OR inflammatory) AND (optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND thickness.
8. ("Bacterial Infections and Mycoses"[Mesh]) OR "Parasitic Diseases"[Mesh]) OR "Virus Diseases"[Mesh]) AND (optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND thickness.

((Infection or infections or infectious or tuberculosis or TB or HIV or human immunodeficiency virus)) AND ((optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND thickness).

9. (optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND thickness AND systemic.
10. (optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND (((((retina or retinal))AND thickness AND ("Nerve Fibres/drug effects"[Mesh:NoExp] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR "Steroids/adverse effects"[Mesh] OR

"Pharmaceutical Preparations/adverse effects"[Mesh])(optical coherence tomography OR optical coherence tomographic OR oct) AND (nerve fibre layer OR nerve fibre layer OR rnfl) AND ((((retina or retinal)) AND thickness) AND (steroids or corticosteroids or steroid or corticosteroid or glucocorticoid or glucocorticoids or ethambutol or vigabatrin or chloroquine or isotretinoin).