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# GLAUCOMA, DEPRESSION AND QUALITY OF LIFE: MULTIPLE COMORBIDITIES, MULTIPLE ASSESSMENTS AND MULTIDISCIPLINARY PLAN TREATMENT

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## SUMMARY

**Background:** The present mini review evaluates assessment and comorbidity of glaucoma and depression with the possibilities of treatment options.

**Subjects and methods:** Web of science was searched for relevant articles using search terms "glaucoma", "depression", "glaucoma and depression", "quality of life and glaucoma". The additional relevant papers were added from the bibliography of selected papers. All types of articles were included, no time period was defined.

**Results:** We have reviewed 11 studies regarding the comorbidities of glaucoma and depression. The number of participants in all studies ranged from 86 to 6760. Formats of scale in one study was clinician rated, others were self-reported scales. Two studies of the above mentioned studies explored specific types of glaucoma. In the three studies out of 11 there was no significant evidence of elevated depressive symptoms associated with glaucoma. In the six studies the prevalence of depression was significant among glaucoma patients. One study provided suboptimal assessments of depression in glaucoma patients. The other one showed the presence of glaucoma significantly associated with depression after adjustment for the demographic factor. Most of the studies used one scale, while two of them used two scales. The reviewed studies did not analyze the therapy options of included patients.

**Conclusion:** The results presented in this review indicate that glaucoma is accompanied by depression in the majority of analyzed studies. The comorbidity of glaucoma and depression should be the subject of further research on both, self-reflecting and clinician-rated scales, taking into account subjective experience of patients and physicians. The therapy options should be taken into account in future researches focusing on the multidisciplinary approach including novel possibilities of treating both diseases respectively.

**Key words:** glaucoma – depression – comorbidities - scales

\* \* \* \* \*

## Introduction

Glaucoma is a chronic, progressive, heterogeneous optic neuropathy which leads to visual field loss, disabilities and irreversible blindness if not diagnosed and treated at the right time. Glaucoma firstly affects peripheral vision and secondly central vision. Since it is silent, chronic disease with no clinical signs at the beginning of illness, it is often undiagnosed and underestimated (Eramudugolla et al. 2013). In many cases when diagnosed, glaucoma is already in advanced stage. Clinical trials confirmed the importance of intraocular pressure (IOP) in the development and progression of open-angle glaucoma, even if evidence suggests the existence of ocular and systemic factors, in addition to IOP, that can be responsible for this development and progression (Actis et al. 2016). These various risk factors may be organized into various categories (Agorastos & Huber 2011, Nageeb & Kulkarni 2015): demographic (age, sex and race), lifestyle (smoking, alcohol), comorbidities (heart disease, peripheral hypertension,

diabetes, obesity), ophthalmic risk factors (eye structure, central corneal thickness, corneal hysteresis, intraocular pressure, myopia, cataract, vascular abnormalities), family history, socioeconomic status and compliance (Salowe et al. 2015). The point is that the main risk factor is ocular pressure (it is also the only one we can treat today), then we can discuss upon the others. In general, patients with visual impairment have higher prevalence of psychological disturbance – such as depression, anxiety or sleep disorders (Agorastos et al. 2013, Eramudugolla et al. 2013, Rovner et al. 2014, Skalicky & Goldberg 2008). It was shown that the strongest connection between psychological disturbances and visual impairment disorder was depression (McCusker & Koola 2015, Actis et al. 2016, Spinelli et al. 1998). The level of depressive symptoms is higher in patients with multiple eye disease (Eramudugolla et al. 2013, Pop-Jordanova et al. 2014). Dual sensory loss, such as visual and hearing impairment, increases even more the level of depressive symptoms (Kiely et al. 2013). On the other hand, depression is one of the most

common psychological disturbances among patients that is comorbid with other chronic physical diseases in general (Jeong et al. 2016, Moussavi et al. 2007) with the most negative effect on the health score. Depression has also higher prevalence among older population (Skalicky & Goldberg 2008). The risk factors for the development of psychological disorders in glaucoma patients could be subjective and objective (Kong et al. 2014). The age, sex, visual field loss (VFL) and the severity of glaucoma condition are some of the objective risk factors on which the patients have no influence (Kong et al. 2014). The subjective risk factors, such as regular and proper administration of topical antiglaucoma medication, education and proper understanding of character of the glaucoma disease or adoption of healthy habits, could be influenced by patients. In the study among the Chinese patients, the comprehension of the character of glaucoma is an independent factor negatively related to psychological disturbance and positively related to the Quality of Life (QoL) among the glaucoma patients (Kong et al. 2014). The authors emphasize the value of education in establishing the healthy habits (the importance of compliance with the therapy) among the patients. The knowledge of glaucoma character with consequent understanding of the value of therapy compliance decreased psychological disturbance and contributed to the higher QoL. In the paper of Agorastos et al, visual field defects (VFD) were predictive factors of depression, anxiety and sleep disorder (Agorastos et al. 2013). The loss of everyday life abilities (driving the car, reading, moving indoors and outdoors, depending on the help of others) could be an important factor in developing depression in glaucoma patient.

## Methodology

The literature search was performed by using PubMed and MEDLINE. The searched terms were “glaucoma”, “depression”, “glaucoma and depression”, “quality of life and glaucoma”. This mini review was limited to the articles published in English language. All types of relevant articles were included in the review, including the original research, reviews and other articles of interest. The additional relevant papers were added from the bibliography of selected paper. The time period was not defined.

## Pathophysiology of glaucoma and depression

Ophthalmic risk factors for glaucoma onset and development are: first of all intraocular pressure (IOP), followed by eye structure (angle of the anterior chamber), central corneal thickness, myopia, cataract, and vascular abnormalities (Salowe 2015). The important pathophysiological mechanism of glaucoma is redundant retinal oxidative stress (ROS) with the consequence on glaucomatous changes and neurodegeneration. The result is the loss of the intrinsically

photosensitive retinal ganglion cells (ipRGC) with consequent disorder in melanopsin activity (Agorastos & Huber 2011), disruption of circadian rhythm and neuropathy of optic nerve (Agorastos et al. 2013, Agorastos & Huber 2011, Ayaki et al. 2015). Consequently, the role of neurohormone melatonin (MLT) in the eye may be involved in the physiology and pathophysiology of retinal function (Agorastos & Huber 2011, Tosini et al. 2012). MLT has a potential use in the management of glaucoma (Agorastos & Huber 2011) as protector against oxidative stress in neurons, antioxidant in the retina, with direct effect on intraocular pressure (IOP) and interference on other glaucomatous risk factors (hypertension, diabetes).

MLT has also an important role in the regulation of circadian rhythm by modulating electrical activities of neurons of suprachiasmatic nucleus. Changes in circadian system or chronodisruption can have an effect on sleep disturbance, seasonal affective disorders and depressive disorders (Tosini 2012). Pathophysiology of depression is not unique and clearly defined. It was shown that serotonin (Dell'Osso 2016), norepinephrine, glutamate and dopamine have an important role in pathophysiology of depressive disorders (Niciu et al. 2014). Recent researches indicate that MLT might have an important role in pathophysiology and possible therapy in many diseases, such as depression, diabetes, pain, neurodegenerative diseases, circadian and mood disorders, insomnia (Comai & Gobbi 2014), and vision disorder such as glaucoma (Agorastos & Huber 2011, Tosini 2012). MLT is synthesized from serotonin and acts through MT1 and MT2 receptors (Agorastos & Huber 2011, Comai 2014). In the study of Comai and Gobi MT2 receptors were involved in the pathophysiology and pharmacology of depression (Comai & Gobbi 2014). In addition, MT1 and MT2 receptors were identified in mammalian retina (Tosini et al. 2012). Therefore, MLT might be connected with reducing of IOP (Tosini et al. 2012). Pathophysiological connection between depression and glaucoma might origin from the reduced absorption of light because of retinal disruption which leads to irregular melatonin synthesis as it was showed in various animal models (Tosini et al. 2012). The result is higher prevalence of depression, anxiety, and sleep disorder.

There is no clear evidence of effectiveness of neuroprotective agents on progression of OAG (Sena & Lindsey 2017). Further clinical researches should plan to explore the benefits of neuroprotective agents on OAG and preservation of vision.

## Epidemiological data

The epidemiological studies indicated an increase in the prevalence of glaucoma (Vost et al. 2015, Boyers et al. 2015, Ferrari et al. 2010, Tham et al. 2014, Wang et al. 2012). In 2013, 64,3 million people with glaucoma (aged between 40 and 80 years) were estimated. It is

calculated that the number of people with glaucoma will have increased up to 76,0 million by the year 2020 and up to 111,8 million by the year 2040 respectively (Tham et al. 2014). Since glaucoma affects mostly older population, whose prevalence has been significantly increased (Skalicky et al. 2015), it presents one of the global public health issues (Tsai et al. 2004, Chen et al. 2015). Global Burden of Disease Study 2013 had ranked the glaucoma prevalence with total percentage of 1.29% in 1990, 1.41% in 2013, while the YLD (years lived with disabilities) ranked 3,58% in 1990, and 4.02% in 2013. Glaucoma prevalence by severity was ranked in the same study in 2013; moderate 0.94%, severe 0.13% and blind 0.34% (Vost et al. 2015). The same study indicated significant percentage change in prevalence of glaucoma from 1990 to 2013 (50.2% vs 74.7%) respectively, the significant changes are YLD from 1990 to 2013 (54.8% vs 70.9%) and in age-standardized YLD from 1990 to 2013 (-9.7% vs -0.2%) (Vost et al. 2015). Glaucoma and macular degeneration global burden were overrepresented according to the Global burden of eye and vision disease as reflected in the Cochrane Database of Systematic Reviews (Boyers et al. 2015). This finding might suggest that certain diseases such as glaucoma attract much more attention of researchers than others, because of their importance in causing morbidity and disabilities.

The results of Moussavis' research, World Health Study (WHS) by World Health Organization (WHO), showed that one-year prevalence of depressive episode was 3.2 % in the 60 countries involved in research (Moussavi et al. 2007). In the case of comorbid depression (depression with chronic physical disease) the prevalence was significantly higher, between 9.3% and 23.0%. Depressive disorders were the second leading cause of YLD according to Global Burden of Disease Study 2010 (Ferrari et al. 2013) and 2013 (Vost et al. 2015, Global Burden 2013, Kessler & Bromet 2013).

According to the findings of several studies, (Wang et al. 2012, Mabuchi et al. 2012, Skalicky & Goldberg 2008) which were undertaken worldwide, the prevalence of depression among glaucoma coincides. The prevalence of depression among glaucoma patients in the study of Wang et al. was 10.9% (Wang et al. 2012) as it was in the Japanese Clinical study (Mabuchi et al. 2012). The range of the prevalence of depression in glaucoma patients was between 11.4% and 32.1% in the Australian clinical study performed by Skalicky et al and Goldberg (Skalicky & Goldberg 2008).

### **The quality of life of glaucoma patients with depression**

The concept of QoL in the last decades has become the focus of interest of many physicians, especially those who treat the chronic disease patients (Labiris et al. 2011). To comprehend the concept of QoL and its purpose in diagnosing and treatment of patients, the re-

searchers need to be aware of the parameters that comprise it: physical, functional, social, and psychological (Labiris et al. 2011). The comorbidity of depression and glaucoma interfere with all of them (Moussavi et al. 2007, Skalicky & Goldberg 2008). In the practice there are several instruments available (Severn et al. 2008, Labiris et al. 2011, Waisbourd et al. 2015, Spratt et al. 2008, Valderes et al. 2004, Brown et al. 1998) for the assessment of the QoL of glaucoma patients that can be divided in three groups: Health related QoL, vision-specific QoL, and disease specific QoL – glaucoma specific instruments. Glaucoma specific tools have higher specificity for glaucoma. According to the literature (Labiris et al. 2011, Severn et al. 2008, Spratt et al. 2008), there are no ideal or generally used QoL instruments for glaucoma. But regardless of that, most of the conducted studies showed that glaucoma patients have lower QoL scores and less functional status (Tsai et al. 2003, van Gestel et al. 2010, Wilson et al. 1998). It was shown that the visual impairment limits the QoL of patients (Skalicky et al. 2015, Labiris et al. 2011). The depression comorbid with chronic conditions such as glaucoma worsen the health status of patients (Moussavi et al. 2007) and have negative implication on the QoL. It was shown that the age related eye diseases like glaucoma are associated with poorer health related quality of life (HRQoL) (Li et al. 2011, Tsai et al. 2004) by worsening poor general health, physical and mental unhealthy days such as limitation of daily activities. Contrary, HRQoL did not deteriorate in glaucoma patients in the study of Esteban et al. (Esteban et al. 2008). Deterioration of glaucoma with VFL is associated with the loss in glaucoma-specific QoL and general health QoL (van Gestel et al. 2010). As the last study indicated, two types of QoL instruments (general health and glaucoma-specific instruments) might be used to assess the proper QoL in glaucoma patients.

### **Assessment of depression in glaucoma patients**

The analyzed literature in this paper provides an overview of instruments used for assessment of depression in glaucoma patients (Gothwal et al. 2014, Cumurcu et al. 2006, Skalicky & Goldberg 2008, Wang et al. 2012, Ayaki et al. 2015, Kiely et al. 2013, Eramudugolla et al. 2013, Wilson et al. 2002, Agorastos et al. 2013, Kong et al. 2014). The screening of the depression like disorder, diagnose of the disorder, assessment of severity of disorder, and the measurement of changes in severity of disorders represent the main purpose of assessment of the scales for depression (Furukawa 2010). The psychiatric assessments can be organized in two formats: clinician-rated and self-report (Furukawa 2010).

Hamilton Depression Rating Scale (HDRS) is clinician-rated scale with 21 items for assessing the severity and measuring the changes of depression (Furukawa 2010, Cumurcu et al. 2014).

**Table 1.** The comparison between reviewed studies based on the assessment of depression, format of rating scales for depression, format of glaucoma assessment and total number of participants

Reviewed studies	Assessment of depression in glaucoma patients		Format of rating scales for depression		Glaucoma assessment		Number of participants in studies		
	Yes	No	Self report	Clinician rated	Scales	Self reported	Objective visual tests	Total N	Glaucoma Patients N
Depression in Patients with Glaucoma as Measured by Self-report Surveys	+	+	+		CES-D; CIDI-SF		+	298	121
Dual sensory loss and depressive symptoms: the importance of hearing, daily functioning, and activity engagement		+	+		CES-D		+	1611	?
Co-morbidity of depression and anxiety in common age-related eye diseases: a population-based study of 662 adults		+	+		GADS	+		750	23
Depression in ophthalmological patients	+		+		BDI-II		+	100	10
Depression, anxiety, and disturbed sleep in glaucoma	+		+		BDI-II		+	86	86
Depression and quality of life in patients with glaucoma: a cross-sectional analysis using the Geriatric Depression Scale-15, assessment of function related to vision, and the Glaucoma Quality of Life-15.	+		+		GDS-15		+	199	165
High prevalence of sleep and mood disorders in dry eye patients: survey of 1,000 eye clinic visitors	+		+		HADS		+	1000	109
Depression and anxiety in patients with pseudoexfoliative glaucoma	+			+	HDRS MADRS		+	113	73
Anxiety and Depression are More Prevalent in Primary Angle Closure Glaucoma Than in Primary Open-Angle Glaucoma.	+		+		SDS			150	100
The patient health questionnaire-9: validation among patients with glaucoma	/	/	+		PHQ-9		+	198	198
Prevalence and predictors of depression among participants with glaucoma in a nationally representative population sample	+/-	+/-	+		PHQ-9		+	6760	453

Montgomeri-Asberg Depression Rating Scale (MADRS) is clinician-rated instrument created with the purpose of measuring the severity and changes of depression (Furukawa 2010, Cumurcu et al. 2006).

Center for Epidemiological Studies Depression Scale (CES-D) is 20 item, self-report instrument which responses are based on depression symptoms experienced one week before the testing. It is used for epidemiological studies of depression in population (Wilson et al. 2002, Kiely et al. 2013).

Composite International Diagnostic Interview-Short Form (CIDI-SF) scale was originally constructed by WHO for assessment of mental disorder. CIDI-SF assesses 8 of 9 symptoms for diagnosing the depressive episode (criteria of Diagnostic and Statistical Manual of Mental Disorder, 4<sup>th</sup> Edition of American Psychiatric Association) (Gigantesco & Morosini 2008, Wilson et al. 2002).

Hospital Anxiety and Depression Scale (HADS) is self-report, created to detect anxiety and depression. It is broadly used in hospital-based surveys, (Kong et al. 2015, Ayaki et al.). It contains two subscales (depression and anxiety), both with 7 items. The answers are based on the relative frequency of symptoms over the past week.

Beck's Depression Inventory-Second Edition (BDI-II) is 21 item self-report and possible self-scored scale for screening of severity and measuring of changes in depression (Furukawa 2010, Agorastos et al. 2013, Pop-Jordanova et al. 2014).

Goldberg Anxiety and Depression Scales (GADS) is self-completed, 18 item questionnaire designed for measurements of the anxiety and depression (9 anxiety and 9 depression items) (Koloski et al. 2008g, Eramudugolla et al. 2013).

Patient-Health Questionnaire (PHQ)-9 is 9 item, self-report version of Primary Care Evaluation of Mental Disorders (PRIME-MD) developed in 1999 (Furukawa 2010, Wang et al. 2012, Gotwall et al. 2014). The purpose of PHQ-9 is self-reported screening of depression, measuring of severity and measuring of changes in depression. The responds are ranked based on the frequency of depressive symptoms over the previous two weeks. In the analyses of validity for screening PHQ-9 showed substantial heterogeneity which was not explained (Furukawa 2010). PHQ-9 provided suboptimal assessment of depression in glaucoma patients in India, in Study of Gothwal et al. (Gotwall et al. 2014).

Geriatric Depression Scale-15 (GDS-15) is self-report instrument with 15 items used to assess depression in elderly population (Skalicky & Goldberg 2008).

Self-rating Depression Scale (SDS) is 20 item, self-reported scale, used to assess affective, psychological and somatic symptoms associated with depression. The responses are ranked according to the frequency of symptoms in the past several days (Kong et al. 2015).

## Depression and glaucoma – studies

On the basis of the above mentioned scales, 11 studies were extracted in this review. The prevalence of depression in patients with visual impairment is the issue of research in many studies (Ayaki et al. 2015, Eramudugolla et al. 2013, Wang et al. 2012, Skalicky & Goldberg 2008). For example, in four of the extracted studies the prevalence of depression in glaucoma patients was significantly higher (Ayaki et al. 2015, Pop-Jordanova et al. 2014, Agorastos et al. 2013, Skalicky & Goldberg 2008). The HADS score for depression was the highest in glaucoma patients in comparison to other patients with visual impairment in the study of Ayaki et al. (Ayaki et al. 2015). This study was primary designed for the assessment of prevalence of sleep and mood disorders in the eye clinic patients. The total number of participants was 730, only 109 of them were glaucoma patients (e.g. Table 1). The severity of glaucoma and older age of the patients, in the study of Skalicky and Goldberg, contributed to higher prevalence of depression in glaucoma patients (Skalicky & Goldberg 2008). The purpose of this study was also to determinate the association of depression and the QoL in glaucoma patients. Glaucoma specific instrument Glaucoma Quality of life-15 (GQL-15) was used for the QoL assessment. The results showed decreased quality of life with worsening severity of glaucoma. The total number and share of glaucoma patients are shown in the table 1. The increasing trend of depression in this study might be due to decrease of central and peripheral vision with consequent reduction of subjective and objective visual function. In the study of Agorastos et al, the VFL in glaucoma was the principal predictive factor of depression (Agorastos et al. 2013) and other psychological disturbances. One of the main messages of this study is the necessity of screening for psychological disturbance and psychochronobiological treatment of glaucoma patients. The importance of regular screening for depression in glaucoma patients supports also the findings of the study of Pop-Jordanova et al, which show that depression was often unrecognized and untreated problem (Pop-Jordanova et al. 2014). The prevalence of depression was often higher in the patients with severe ophthalmological disturbances (glaucoma, age-related macular degeneration, proliferative diabetic retinopathy and cataract) in the study of Pop-Jordanova (Pop-Jordanova et al. 2014) which is consistent with the study of Skalicky and Goldberg (Skalicky & Goldberg 2008). In addition the level of depression was found higher in the elderly population which is in coincidence with both the above mentioned studies (Skalicky & Goldberg 2008, Pop-Jordanova et al. 2014).

The two papers from this review reported comorbidity of specific type of glaucoma and depression (Cumurcu et al. 2006, Kong et al. 2015). The study of Cumurcu et al, discussed the association of pseudoexfoliative glaucoma (PXG) and depression (Cumurcu et al. 2006). The PXG patients were more depressed then

patients with primary open angle glaucoma (POAG) and control group. The same study showed no significant differences in the anxiety scale comparing PXG or POAG group respectively, and the control groups. The higher level of depression was associated with the patients with primary angle closer glaucoma (PACG) in contrast to patients with POAG and control group in the study of Kong et al. (Kong et al. 2015). Both studies compared POAG with other types of glaucoma and both studies showed that patients with POAG were less depressed. However, on the basis of these two studies, it could not be possible to conclude that POAG patients are less depressed than patients who suffer from other types of glaucoma. The existence of association of certain type of glaucoma and depression (Cumurcu et al. 2006, Kong et al. 2015) should be evaluated in further studies.

In the three studies (Eramudugolla et al. 2013, Wilson et al. 2002, Kiely et al. 2013), there were no significant correlation between depression and glaucoma. Eramudugolla et al. associated such findings with self-reported knowledge of glaucoma that might have compromised the result because glaucoma is often underdiagnosed in population (Eramudugolla et al. 2013), which is consistent with the previous study of Pop-Jordanova (Pop-Jordanova et al. 2014). The same indicates the study of Kiely et al, e.g. there is no increase of depression in patients with only visual field loss (corrected distance visual acuity > 0,3 longMar in the better eye, self-reported blindness and glaucoma) (Kiely et al. 2013). The glaucoma patients did not report higher depression than patients without glaucoma in the study of Wilson et al. (2002).

Finally, the last two studies from this review, which used PGQ-9 scale, did not have congruent results (Wang et al. 2012, Gothwal et al. 2014). PHQ-9 instrument in the study of Gothwal et al. with 198 patients did not provide optimal assessment of depression in glaucoma patients (Gothwal et al. 2014). In the study of Wang et al. (2012), where the PHQ-9 scale was also used, the presence of correlation between depression and glaucoma had no significance without the adjustment. The authors used two models of adjustments: adjustments for demographic factors and for the self-report of the general health condition. The model in which glaucoma and depression were adjusted for the demographic factors, the association of glaucoma and depression, was significant. The model with adjustment for the general health condition found no significant correlation with glaucoma and depression. We can calculate that PHQ-9 is not the instrument of choice for the assessment of depression in glaucoma patients. On the other hand, Furukawa reported (Furukawa 2010) PHQ-9 as an instrument with excellent psychometric properties but with substantial heterogeneity in screening validity, which could not be explained.

There are no unique results of the studies regarding the association of depression with glaucoma (McCusker & Koola 2015, Kiely et al. 2013, Wilson et al. 2002,

Tosini et al. 2012, Eramudugolla et al. 2013, Skalicky & Goldberg 2008) using different measurement instruments (e.g. Table 1). Table 1 recapitulates the comparison between reviewed studies based on the assessment of depression, format of rating scales for depression, format of glaucoma assessment and the total number of the participants with the share of glaucoma patients (e.g. Table 1). Only one study used clinician-rated scales (HDRS and MADRS) for the assessment of depression in glaucoma patients (Cumurcu et al. 2006). Most of the studies used objective visual tests for glaucoma assessment. Only in two studies glaucoma was assessed by self-report method (Eramudugolla et al. 2013, Wang et al. 2012). In the first study, there was no evidence for elevated rates of depression in glaucoma (Eramudugolla et al. 2013). The total number of participants and the number of glaucoma patients varied widely among reviewed studies (e.g. Table 1). The total number of participants ranged from 6760 to 86. The range of glaucoma patients varied from 10 to 453. In one study the number of glaucoma patients was unknown (Kiely et al. 2013). Some of the studies were performed only with the glaucoma patients (Gothwal et al. 2014, Agorastos et al. 2013), while others had combination of patients with visual impairment, control group. One of the issues which could have influenced the results was the range of glaucoma patients in the study.

### **Management of patients who suffer from glaucoma and depression**

The aging of population, the increase in various comorbidities, the various available medications and the organization of health care pose a great challenge for clinicians in the management of chronic patients today.

By focusing only on the treatment of glaucoma, comorbidities are often neglected. Depression as a comorbid condition deteriorates the health of the patients more than depression alone or more than other chronic conditions, alone or in combination of different chronic diseases without depression (Moussavi et al. 2007). Chronic conditions such as glaucoma may be associated with depression due to the age of patients (Jeong et al. 2006, Kong et al. 2014), prolonged daily use of antiglaucoma medications, limitation of daily activities, limitation of family and working roles (Guedes et al. 2012).

The antiglaucoma medication is mostly topical application. The possibilities of systematic adverse effects are uncommon but they are still possible (Jeong et al. 2016). For example, the caution with regard to use of ocular beta-blockers was recommended in the case of depression, asthma and heart disease. However, recent studies did not find any correlation between beta-blocker use and depression (Wilson et al. 2002). The recent studies have also suggested that phenylephrine eye drops had no clinically relevant effects on the heart rate or blood pressure as was previously suggested (Stavert et al. 2015).

The topical administration of antiglaucoma medications, on the other hand, has very common topical side effects (Guedes et al. 2012, Servat & Bernardino 2011, Park et al. 2013) such as eyelid dermatitis, lacrimal system scarring, ocular discomfort upon instillation, conjunctival inflammation and conjunctival epithelium changes, corneal surface and endothelial impairment, blurred vision, a stinging sensation etc. The patients diagnosed with glaucoma during the period when the symptoms of visual field and visual function loss had not still been developed, could only experience the disturbing side effects of antiglaucoma therapy. As a result, some of the early diagnosed glaucoma patients might give up on therapy. The initial education of patients regarding the possibilities of side effects of the antiglaucoma therapy and the severe consequences of nonadherence to it is very important (Park et al. 2013).

The price of medications, the difficulties with administration and dosing schedule might contribute to poor compliance, worsening IOP, and consequently depression. The patient is in vicious circle.

The different situation with the same result appears in patients with good compliance, sometimes multiple ophthalmological therapy (surgery and multiple medications), regular follow-ups, with the result of advanced glaucoma and VFL with the respond of depression (Gothwal et al. 2014).

Administration of psychiatric medication can cause glaucoma (Jeong et al. 2016). Tricyclic antidepressants can lead to closed-angle glaucoma because of anticholinergic activity. Because of epinephrine receptor blockade, some of the antipsychotic drugs can also cause closed-angle glaucoma. Selective serotonin inhibitors and benzodiazepines can generate in closed-angle glaucoma. Long-term use of selective serotonin reuptake inhibitors (SSRI), which are the most prescribed type of medication for depression, does not significantly influence the risk of POAG and PACG (Chen et al. 2015). One of the future possibilities in the management of comorbidity of glaucoma and depression is MLT, as it was described in the papers of Agorastos and Huber (Agorastos & Huber 2010), and Tosini et al. (Tosini 2012).

The character of depression with the hopelessness and pessimism may cause poor compliance and withdrawal of the therapy (Jeong et al. 2016).

Besides the standard therapy of glaucoma, topical antiglaucoma medications and surgery, novel approaches such as melatonin (Agorastos & Huber 2011, Tosini et al. 2012), endocannabinoid system (Cairns et al. 2016), and bone-marrow mesenchymal stem cell (Roubeix et al. 2015) should be explored.

Cognitive deficits are often comorbid with depression (Joeng et al. 2016). Due to cognitive deficit the patients are not able to comprehend the character of glaucoma and the necessity of adherence to the therapy which leads to worsening of glaucoma and blindness.

The management of the patients with comorbidity of glaucoma and depression should be organized on the basis of a multidisciplinary approach (Jeong et al. 2016). An ophthalmologist has to recognize and take into account a state of depression when the treatment plan is made (Moussavi et al. 2007).

The organization of health care in the case of subspecialist glaucoma ambulance is an important factor in the management of glaucoma patients (the time for the review; education about the characteristics of glaucoma, possibilities and side effects of treatment; the real role of glaucomatologist, the role of a subspecialty nurse). The next step should be the involvement of a multidisciplinary team consisting of psychologists, psychiatrists and rehabilitation therapists (Rovner et al. 2014).

## Conclusion

The results presented in this review indicated that glaucoma is accompanied by depression in the majority of analyzed studies. The rating scales used in assessing depression in studies analyzed in this review had different purposes and different formats. The questionable is connection of formats of instruments used in the studies (self-reporting or clinician-reporting) and assessments or no assessment of depression. Besides the issues of different instruments, formats of assessments and the number of participants in the studies, subjective experience of patients and physicians should be taken into account when assessing the depression in glaucoma patients (Wang et al. 2012). The reviewed studies did not analyze therapy options of glaucoma patients with depression. The treatment of comorbidity of glaucoma and depression should not depend only on ophthalmologist or psychiatrist, the assessment of treatment should be multidisciplinary. New approaches, such as MLT administration, should be taken into account in the management of glaucoma patients with depression. The management of glaucoma and depression should be comprehended as a public-health issue because of epidemiological data regarding the rising prevalence of both chronic diseases worldwide.

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## Contribution of individual authors:

Goran Pelčić: concept and design of study, drafting the manuscript, critical revision for intellectual content, supervision;

Rudolf Ljubičić: drafting the manuscript, critical revision for intellectual content;

Josip Barać: literature searches and analyses, critical revision for intellectual content;

Dubravka Biuk: interpretation of data, critical revision for intellectual content;

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