Drug-Induced Deficits in Color Perception: Implications for Vision Rehabilitation Professionals

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Along with the aging of the population, various comorbidities may arise, such as arthritis, hypertension, and erectile dysfunction (Glynn, Monane, Gurwitz, Choodnovskiy, & Avorn, 1999; Ramage-Morin, 2009). These medical conditions are treated and controlled with various types of medications. In fact, nearly 83% of older adults in Canada take prescription medications by age 65 years. Several of these medications can induce subtle side effects, including decreased visual perception. For instance, previous research indicated that side effects of commonly prescribed type-5 inhibitors (such as Viagra) may include declines in color perception (Azzouni & Abu Samra, 2011; Santaella & Fraunfelder, 2007).

Many health care professionals, including vision rehabilitation therapists (VRTs), should be aware of the possibility of drug-induced deficits in color perception when working with older adults. The main purpose of this report is, therefore, to identify the commonly prescribed medications for age-related conditions that disturb color vision, and highlight the colors that are most frequently affected by these medications. This report aims to provide professionals who work with older adults with guidelines on how to identify individuals at risk for acquired color deficits and how to consider these insufficiencies during various rehabilitative interventions.

A scoping review of the literature was conducted to identify the most commonly prescribed medications for age-related conditions like arthritis that can potentially alter color perception. An advanced search in the following databases was conducted: PubMed, EBSCO, and Google Scholar. The main Medical Subject Heading (MeSH) terms that were used in combination in searching for peer-reviewed articles included: acquired color deficits, drug-induced color deficits, side effects, medications, color vision, drug toxicity, hydroxychloroquine, type-5 inhibitor, plaquenil, ocular adverse effects, and retinal toxicity. Key words found in relevant articles were added to the search terms. In addition, Boolean terms such as *and* and *or* were used to refine the quest for relevant articles.

Medications affecting color vision

Color perception is made possible by three cone cell types embedded in the retina that are preferentially sensitive to different wavelengths of light. The S-cones are sensitive to short wavelengths (420 nanometers [nm]; also known as blue-cone). A deficit or absence in S-cones results in tritanopia, causing a blue-yellow color deficit or blindness. Similarly, the M-cones are sensitive to medium wavelengths (535 nm; also known as green-cone) and the L-cones to long wavelengths (565 nm; also known as red-cone). The absence of M- or L-cones results in deuteranopia or protanopia, respectively. A deficit in any cone type results in a decreased ability to detect color hues. Given that the eye is a high-metabolism organ that contains many blood vessels, it is susceptible to the effects of systemic medications (Santaella & Fraunfelder, 2007). It was long thought that congenital color deficits were more common than acquired ones. In fact, approximately 8% of males and 0.5% of females are diagnosed with a congenital color deficit (Simunovic, 2010). However, some researchers argue that acquired color deficits are more prevalent than previously thought; a study conducted in North America revealed that the prevalence rate is 20.8% for older adults between ages 58 and 102 years (M = 75.2) (Simunovic, 2016).

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The effects of acquired color deficits can vary widely. For instance, some may develop problems in the red-green color axis (deuteranopia/protanopia), and others in the yellow-blue axis (tritanopia). Nevertheless, the most common type of acquired color deficit is in the blue-yellow axis. An Iranian study revealed that 66.1% of acquired color deficits result in tritanopia (Jafarzadehpur et al., 2014). There are several causes for declines in color perception, but the most common ones are natural decline with age or as a result of medication intake (Delpero, O'Neill, Casson, & Hovis, 2005).

Six drug types frequently prescribed to seniors that can potentially alter color perception were identified. Lanoxin, known under the generic name Digoxin, is commonly used to treat various heart conditions. This drug is a cardiac stimulant, increasing the strength and efficiency of the heart muscle (Lawrenson, Kelly, Lawrenson, & Birch, 2002). It is often used to treat conditions such as arrhythmia (arterial fibrillation). The risk of developing arrhythmia increases with age and is strongly associated with other age-related conditions such as hypertension and diabetes (Du et al., 2009). Moreover, Lanoxin consumption has been associated with xanthopsia, a condition that results in yellow-tinted vision due to yellowing of the optic media or lens of the eye (Carlson & Buck, 2002). It has also been associated with tritanopia, making color pairs such as green-blue, as well as yellow-violet, difficult to discriminate (Lawrenson et al., 2002). Similarly, Lasix (Furosemide) is a diuretic often prescribed in combination with hypertension medication and can cause yellow-tinted vision (Carlson & Buck, 2002).

Hydroxychloroquine, commonly known as Plaquenil, is another drug that can result in color vision alterations. Plaquenil is an antimalarial drug that is at times prescribed for rheumatoid arthritis (Santaella & Fraunfelder, 2007). It has been estimated that 50.6% of women and 33.8% of men ages 65 or older have an arthritis diagnosis. These percentages increase to 53% for women and 40% for men by 75 years of age (Statistics Canada, 2015). Therefore, it is likely that many seniors take arthritis medication to reduce inflammation and pain. Santaella and Fraunfelder (2007) reported that Plaquenil can result in deficits in the yellow-blue axis of the color spectrum, making blue and green, as well as yellow and violet, difficult to discriminate.

Sildenafil, commercially known as Viagra, is another drug that can alter color vision and is frequently prescribed to older men. In fact, it has been estimated that 42% of men aged 60 to 69 years have moderate to severe erectile dysfunction. Among men aged 70 years or older, the proportion rises to approximately 70% (Grover et al., 2006). The frequency and severity of erectile dysfunction increases with age and is a worldwide occurrence (Nicolosi, Moreira, Shirai, Tambi, & Glasser, 2003). Therefore, many older men take type-5 inhibitors (such as Viagra), which increase blood flow to smooth muscles, resulting in a higher probability of getting and maintaining an erection during intercourse (Stockman et al., 2007). Viagra can result in trouble discriminating colors such as blue, purple, and green, often described by men as "bluish vision." The literature on Viagra is, however, controversial; although some studies show no significant changes in color vision compared to the general population (Azzouni & Abu Samra, 2011), others report color vision alterations (Santaella & Fraunfelder, 2007). But all studies agree that effects of Sildenafil on color vision are transient and reversible (Laties & Zrenner, 2002; Li, Tripathi, & Tripathi, 2008).

Tamoxifen (Nolvadex) is a drug used to reduce the risk of breast cancer. One of the main risk factors for developing breast cancer is age (Yancik, Ries, & Yates, 1989), making this medication more likely prescribed to older women. Approximately 13% of Tamoxifen users report visual changes related to the drug. Similarly to Hydroxychloroquine and Sildenafil, it can also result in blue-yellow axis deficits. In addition, it can result in corneal opacity and cataracts, leading to yellowing vision (Li et al., 2008).

Mechanisms underlying the changes in color vision resulting from medication intake are debated in the literature. Various theories explaining the reasons for which the S-cones are more affected than L- and M-cones in acquired color deficits are well defined in a recent article by Simunovic (2016). It is important to note that drug-induced color deficits resulting from medications are merely a possible side effect. Only a small proportion of older adults taking these drugs experience a decline in color vision. In addition, the undesired side effects are often reversible with drug discontinuation. Drug toxicity is also said to be dose and time dependent; higher doses and longer periods of drug intake increase the risk of developing drug toxicity (Santaella & Fraunfelder, 2007).

Implications for vision rehabilitation professionals

Color-coding interventions in visual rehabilitation

Cooper, Gowland, and McIntosh (1986) indicated that color coding and color highlighting are types of intervention often used in rehabilitation for age-related vision loss (for example, age-related macular degeneration). One example of rehabilitative color-coding for seniors with low vision is fixing a colored sticker on the start button of a microwave to facilitate its localization and identification. If older adults receiving this type of intervention have a drug-induced color deficit, such a color-specific rehabilitation technique may not be optimal, and a focus on high contrast may be more advisable. Thus, it is crucial for VRTs to be aware of colors that are most commonly affected by prescription drugs, allowing more efficient color-coding interventions for clients. Given that most drug-induced color deficits affect S-cones or result in yellowish vision, colors such as blue, green, yellow, purple, and violet should be avoided. Some VRTs use primarily high-contrast colors and tactile stickers in their interventions, allowing vision-impaired patients to use their sense of touch to identify the location of important buttons. Such a type of home intervention is likely unaffected by drug-induced color deficiencies such as tritanopia and xanthopsia, and thus might be the most efficient method for VRTs working with seniors.

Medication discrimination. Many older adults rely on the color of pills to identify and discriminate them, and to know which ones to take and when. Thus, pharmaceutical industries should consider the importance of colors that may be confused and those that are less easily distinguished, in order to decrease the probability of drug-intake errors. It is important to note that many seniors are not aware of their color perception deficits, since they develop gradually and are not apparent to friends and family (Rigby, Warren, Diamond, Carter, & Bradfield, 1991). Even seniors who are not affected by drug-induced color deficits may have difficulties identifying low-contrast, pastel-colored pills, since older adults experience a natural decline in color perception with age (Cooper, Ward, Gowland, & McIntosh, 1991). Therefore, it is in the best interest of pill manufacturers to make medications easily distinguishable. One option is to place greater emphasis on the shape rather than the color of pills. VRTs should assist their patients in addressing this potential problem by ensuring that similarly colored pills are distinguished in another way. For instance, the bottle of pills can be marked with tactile stickers (such as one tactile sticker for morning pills and two for nighttime pills).

Assistive technology. The presence of drug-induced color deficits should also be considered by companies designing assistive technology devices. Seniors often use these devices to facilitate activities of daily living like reading. Thus, it is important to consider that the use of blue, yellow, green, and violet on the buttons and controls of these devices may induce color discrimination issues for those with acquired color deficit. VRTs should ensure that their patients are capable of identifying all buttons on their assistive technology devices, especially when they are meant to be distinguished by color. If this is not the case, tactile stickers can again be used as a code (for instance, one for start and two for stop). There are many other professionals who can benefit from information on colors affected naturally with age or with certain medications. Not only is this information relevant in the domain of health care, but also for many marketing efforts that target seniors. For instance, to highlight nutritious cereals containing low sodium, low sugar, and high calcium, the box design should be displayed in high-contrast colors that most seniors can perceive.

Color vision tests

Most color vision tests were designed to detect red-green color blindness, since it was long thought to be the most common type (Wong, 2011). However, recent studies show that acquired color deficits are more prevalent than believed (Delpero et al., 2005). The most frequently used color tests (such as Ishihara and Farnsworth D-15) have been designed to detect congenital defects and lack the sensitivity to reveal acquired color deficits. There are nonetheless multiple tests created to address this issue. The utility and generalizability of color tests, therefore, should be well understood before testing color vision in seniors taking various systemic medications (some tests are more appropriate to detect acquired color deficits, most often in blue-yellow axis).

City University Test

The City University Test (CUT) is very similar to Farnsworth D-15, but is useful in detecting yellow-blue color deficits (tritanopia). The Farnsworth D-15 test requires good dexterity, since patients are asked to sort small pastels in chromatic order. Instead, the CUT is a 10-page book containing five colored circles on each page, one central reference color, and four testing colors (Hasrod & Rubin, 2015). The patient is required to identify the test color that matches the center reference color. Three other colors lie on the dichromatic confusion lines, one of which is meant to confuse patients with tritanopia. This test has the advantage of not requiring fine dexterity, which is useful when working with older adults.

Cambridge Color Test

The Cambridge Color Test (CCT) is a computer-based test that shares similarities with the Ishihara test. However, the colored plates include identifying blue-yellow axis confusion colors. It is important for the colors of tests to remain constant over time; however, colors that are printed rather than those that are generated by computers can vary slightly over time and affect results. Therefore, the computer-based CCT has the advantage of its colors remaining constant over time. In addition, the difficulty level can be adjusted for each individual patient, making the test suitable for a large array of deficits. During this test, the patient is presented with the letter *C* in a specific luminance and hue, embedded in various backgrounds of colored circles. Patients must identify the orientation of the letter by using a four-alternative forced-choice paradigm: up, down, right, or left (Hasrod & Rubin, 2015). Similar to the CUT, this test does not require manual dexterity.

Color Assessment and Diagnosis

The Color Assessment and Diagnosis (CAD) test is efficient in detecting all three kinds of color vision deficits. Because it is computer based, changes in luminance and contrast over time are controlled. It requires the patient to identify the direction of the moving colored dot on a computer screen, and thus does not necessitate dexterity (Rodriguez-Carmona, Harlow, Walker, & Barbur, 2005), making it suitable to examine drug-induced color deficits in older adults.

Mollon Reffin Test

The Mollon Reffin test is useful in detecting most types of color vision discrimination deficits, including tritan confusions. Interestingly, this test has also been created in a larger format to facilitate detection of acquired color deficits in patients with low vision (Simunovic, 2010).

The list presented here is not an exhaustive inventory of all color tests that can be used to assess acquired loss of chromatic sensitivity, and a more extensive review is available elsewhere (Simunovic, 2016). In addition, these tests can be used alone or in combination. It is up to the clinician to determine the best course of action based on the capacities of each individual.

Conclusion

Most cone photoreceptors responsible for encoding color are found in the macula (the centre of the retina). This region of the eye can degenerate with age, progressively affecting color vision for older adults (Simunovic, 2016). The majority of seniors take multiple types of medications per day for various age-related conditions. In addition to a natural decline in color vision, studies show that a variety of medications can result in color vision deficits as well. It is not uncommon for seniors to be unaware of such color deficits. Thus, it is important for health care professionals to consider the possibility of drug-induced color deficits, and to have the tools to screen for drug toxicity. The color deficits reported from the intake of systemic medications are often in the blue-yellow axis of the color spectrum, which can result in confusion between blue, purple, and green, as well as for between yellow and violet. This information is important for health care professionals working with seniors, as well as for those who market products to this population. To increase the visibility and practicability of their interventions (such as tactile stickers) or products (such as pills), professionals should avoid such colors. The problem of drug-induced color deficits is one that is more prevalent than expected and deserves attention from health care professionals such as VRTs.

References

Azzouni, F., & Abu Samra, K. (2011). Are phosphodiesterase type 5 inhibitors associated with vision-threatening adverse events? A critical analysis and review of the literature. *Journal of Sexual Medicine*, *8*(10), 2894–2903. doi: 10.1111/j.1743-6109.2011.02382.x

Carlson, L., & Buck, M. (2002). *Pharmaceutical agents* (Report). Aleda Lutz Veterans Affairs Medical Center, Saginaw, Michigan.

Cooper, B., Gowland, C., & McIntosh, J. (1986). The use of color in the environment of the elderly to enhance function. *Clinics of Geriatric Medicine*, *2*(1), 151–162.

Cooper, B. A., Ward, M., Gowland, C. A., & McIntosh, J. M. (1991). The use of the Lanthony New Color Test in determining the effects of aging on color vision. *Journal of Gerontology*, *46*(6), 320–324.

Delpero, W. T., O'Neill, H., Casson, E., & Hovis, J. (2005). Aviation-relevent epidemiology of color vision deficiency. *Aviation, Space, and Environmental Medicine*, *76*(2), 127–133.

Du, X., Ninomiya, T., de Galan, B., Abadir, E., Chalmers, J., Pillai, A., Woodward, M., . . . Poulter, N. (2009). Risks of cardiovascular events and effects of routine blood pressure lowering among patients with type 2 diabetes and atrial fibrillation: Results of the ADVANCE study. *European Heart Journal*, *30*(9), 1128–1135. doi: http://dx.doi.org/10.1093/eurheartj/ehp055

Glynn, R. J., Monane, M., Gurwitz, J. H., Choodnovskiy, I., & Avorn, J. (1999). Aging, comorbidity, and reduced rates of drug treatment for diabetes mellitus. *Journal of Clinical*

Epidemiology, *52*(8), 781–790. doi: http://dx.doi.org/10.1016/S0895-4356(99)00055-4

Grover, S. A., Lowensteyn, I., Kaouache, M., Marchand, S., Coupal, L., De Carolis, E., Zoccoli, J., & Defoy, I. (2006). The prevalence of erectile dysfunction in the primary care setting: Importance of risk factors for diabetes and vascular disease. *Archives of Internal Medicine*, *166*(2), 213–219. doi: 10.1001/archinte.166.2.213

Hasrod, N., & Rubin, A. (2015). Color vision: A review of the Cambridge Color Test and other color testing methods. *African Vision and Eye Health*, *74*(1), 1–7. doi: 10.4102/aveh.v74i1.23

Jafarzadehpur, E., Hashemi, H., Emamian, M. H., Khabazkhoob, M., Mehravaran, S., Shariati, M., & Fotouhi, A. (2014). Color vision deficiency in a middle-aged population: The Shahroud Eye Study. *International Ophthalmology*, *34*(5), 1067–1074. doi: 10.1007/s10792-014-9911-2

Laties, A. M., & Zrenner, E. (2002). Viagra (sildenafil citrate) and ophthalmology. *Progress in Retinal and Eye Research*, *21*(5), 485–506. doi: 10.1016/S1350-9462(02)00013-7

Lawrenson, J., Kelly, C., Lawrenson, A., & Birch, J. (2002). Acquired colour vision deficiency in patients receiving digoxin maintenance therapy. *British Journal of Ophthalmology, 86*(11), 1259–1261. doi: 10.1136/bjo.86.11.1259

Li, J., Tripathi, R. C., & Tripathi, B. J. (2008). Drug-induced ocular disorders. *Drug Safety*, *31*(2), 127–141. doi: 10.2165/00002018-200831020-00003

Nicolosi, A., Moreira, E. D., Shirai, M., Tambi, M. I. B. M., & Glasser, D. B. (2003). Epidemiology of erectile dysfunction in four countries: Cross-national study of the prevalence and correlates of erectile dysfunction. *Urology*, *61*(1), 201–206. doi: 10.1016/S0090-4295(02)02102-7

Ramage-Morin P. (2009). Medication use among senior Canadians. *Health Reports, 20*(1), 37–44.

Rigby, H. S., Warren, B. F., Diamond, J., Carter, C., & Bradfield, J. W. (1991). Color perception in pathologists: The Farnsworth-Munsell 100-Hue Test. *Journal of Clinical Pathology*, *44*(9), 745–748.

Rodriguez-Carmona, M. L., Harlow, A. J., Walker, G., & Barbur, J. L. (2005). The variability of normal trichromatic vision and the establishment of the "normal" range. *Proceedings of 10th Congress of the International Color Association, Granada*, 979–982.

Santaella, R. M., & Fraunfelder, F. W. (2007). Ocular adverse effects associated with systemic medications. *Drugs*, *67*(1), 75–93. doi: 0012-6667/07/0001-0075

Simunovic, M. P. (2010). Colour vision deficiency. *Eye, 24*(5), 747–755. doi: 10.1038/eye.2009.251

Simunovic, M. P. (2016). Acquired color vision deficiency. *Survey of Ophthalmology, 61*(2), 132–155. doi:10.1016/j.survophthal.2015.11.004

Statistics Canada. (2015). *Arthritis.* Retrieved from http://www.statcan.gc.ca/pub/82-229-x/2009001/status/art-eng.htm#re

Stockman, A., Sharpe, L. T., Tufail, A., Kell, P. D., Ripamonti, C., & Jefferey, G. The effect of sildenafil citrate (Viagra) on visual sensitivity. (2007). *Journal of Vision*, *7*(8), 1–5.

Wong, B. (2011). Points of view: Color blindness. *Nature Methods*, *8*(6), 441–441. doi: 10.1038/nmeth.1618

Yancik, R., Ries, L. G., & Yates, J. W. (1989). Breast cancer in aging women. A population-based study of contrasts in stage, surgery, and survival. *Cancer*, *63*(5), 976–981. doi: 10.1002/1097-0142

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