Cannabis and the Visual System

Denise A. Valenti, OD, FAAO

Author’s Bio

Dr. Denise A. Valenti is a residency-trained, low-vision/blind-rehabilitation optometrist with additional education and expertise in the field of age-related neurodegenerative diseases with the emphasis on Parkinson’s disease and Alzheimer’s disease. Dr. Valenti works with cognitive impairment as it relates to driving including induced dysfunctions secondary to cannabis. Dr. Valenti has had additional training as an MGH/MIT/HMS Functional MRI Fellow at the Martinos Center for Biomedical Imaging in Boston, Massachusetts and participated in the yearlong seminar series offered through the Boston University Sleep Disorders Center Fellowship program. Her research has included the study of imaging of retinal neural tissue using Optical Coherence Tomography and functional assessment of neural processing in the visual system using Frequency Doubling Technology. Dr. Valenti provided direct clinical care for more than 25 years and currently is active in research and consultation related to vision, aging, neuroprocessing and cognitive functions. Dr. Valenti currently teaches Low Vision and Geriatrics at the MCPHS University School of Optometry and Gerontology at Quincy College and provides medical content to numerous professional newsletters throughout the United States.

Introduction

Primary care medical providers need to know how cannabis/marijuana impacts their patients. For optometrists this is particularly important as marijuana creates dysfunctions in visual processing and this can have an effect on quality of life and in particular driving an automobile or operating machinery. Marijuana disrupts brain visual processing and induces perceptual dysfunctions. Chronic marijuana use can impair quality of life [1] and those with underlying mental health problems are particularly vulnerable.[2] Additional concerns are how the combination of existing visual dysfunctions related to an underlying disease such as glaucoma, Alzheimer’s disease, Parkinson’s disease or Multiple Sclerosis confounds the visual functional impairments induced by marijuana. Twenty-three states have legal medicinal use of marijuana and four states and the District of Columbia have legal recreational use.[3] It is estimated that there are 1,137,069 registered medical marijuana users and the total number of those using marijuana for medical purposes nationwide is double that. California has more than 75,000 registered medical marijuana users. Marijuana is the most commonly used recreational drug with an estimated 20 million consumers.[4] Very little is known about the short-term and long-term consequences of chronic use of marijuana throughout human development and aging. The studies on humans and the visual system are very few and have limitations. Other models such as cellular and animal must be relied upon in order to gain insight into the impact cannabis use may have on our patients.

Cannabinoids/Cannabis and Visual Neuroprocessing Retina/Brain

The active ingredients in cannabis impact the cannabinoid receptors in the human body. Cannabinoid receptors are throughout the visual pathway.[5] The primary receptors that have been identified are classified as either CB1, and this category is highly represented in the central nervous system; including the retina, or classified as CB2. CB2 receptors are represented in the central nervous system but to a lesser degree and have greatest prevalence in the periphery and immune systems. In humans, there are two primary endogenous compounds acting on the receptors, N-
arachidonylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG). Anandamide acts primarily post-
synaptically as a retrograde compound to modulate neurotransmitters. Anandamide has greater affinity for CB1 receptors. 2-AG has been found to act pre-synaptically and also has greater affinity for CB1 receptors. 2-AG is found abundantly in the brain, but shows less affinity for CB1 receptors than does Anandamide.[5] The receptor sites in the brain related to CB1 and CB2 are primarily those involved in higher cognitive functions; forebrain, midbrain and hindbrain have areas associated with the control of movement; and in hindbrain areas associated with the control of motor and sensory functions of the autonomic nervous system.[6] All regions where cannabinoid receptors have been identified have implications for performance related to driving.
The human retina has representation of cannabinoid receptors throughout multiple layers and cell structures. This is supported by animal models. CB1 activity in the human retina is evidenced by staining in the synaptic layers of the retina; the inner and outer plexiform layers. The density of CB1 receptors increases in the inner nuclear layer and the ganglion cell layer. There is substantial staining in the outer segments of the photoreceptors.[7] Research has demonstrated the expression and regulation of CB1 receptors in human RPE cells.[8] An animal model using mice supports this with identifying CB1 in the inner retina and ganglion cells, with integrations and processing of excitatory signal from bipolar cells and inhibitory signals from amacrine cells.[9] The activation of CB1 receptors differs dependent on the circadian quality of light; night versus daytime. If CB1 receptors are activated during the day, the rod-cone gap junctional signaling is decreased. However, if activated at night the rod-cone gap junctional signaling is increased.[10] This has functional implications for scotopic vision and glare recovery.

An additional rodent model has demonstrated that CB2 receptors are localized in cone and rod photoreceptors, horizontal cells, some amacrine cells, and bipolar and ganglion cells.[11] Additional evidence of CB2 within rodent retina as well as the central nervous system has been identified by additional groups.[12] Lu and colleagues identified CB2 evidence in the somas of retina ganglion cells in a rodent model.[13] This differs from a primate model, which shows that CB2 is in the primate retina but exclusively in the retinal glia, with the model still supporting that CB1 is present in neuroretina. [14]

One of the primary brain nuclei involved in processing visual signals is the lateral geniculate nucleus (LGN) and this area is dense in cannabinoid receptors. A primate model; vervet monkey, shows that CB1 receptors are throughout the LGN with prominent findings in the magnocellular layers and less prominence, but still evident, in the koniocellular layers.[15] Magnocellular functions involve primarily achromatic signal; related to contrast and temporal functioning of vision. The current testing for glaucoma utilizing contrast and temporal functioning is assessing magnocellular processing. Koniocellular functioning involves the processing of chromatic signals in the blue wavelength. Another primate model of CB1 functioning within the LGN demonstrated that the active ingredient in cannabis inhibits cells that would normally fire when exposed to light, and cells that would be inhibited by light were either unresponsive with no inhibition activity or actually had an increase in excitation.[16] This has significant implications for the interaction of central macular retinal functions and peripheral retinal functions as well as scotopic (night or dark) and photopic (day or light) functions.

DaSilva and colleagues were able to quantify the functional action on CB1 receptors within the LGN and found two populations; 28% were excited by an antagonist and 72% were inhibited. When activated artificially (as would be with cannabis) the visual signals were altered. With excitatory activity there was a decrease in the signal to noise, but an increase in variability. With altered inhibition; which accounts for over 70% of the cells in the LGN, there was an increase in the signal to noise with reductions in variability. They concluded that the abnormal signals originating from the LGN with artificial stimulation of the cannabinoid receptors using cannabis and then traveling to the cortex would account for the behavioral effects of cannabis.[17] The findings in the LGN support evidence of diverse roles of cannabinoid receptors in both the retina and the LGN, in modulating both excitation of cells and the inhibitory cell functions. The authors hypothesize that the cannabinoid receptor functions within the visual system account for many of the behavioral effects from cannabis. The behavioral effects and changes in cognitive function along visual pathways, demonstrated by functional brain imaging, are enough to impair driving functions. (MRI) A rodent model of development and function of CB1 receptors in the visual cortex found intense staining for CB1 in layers II, III, and VI. The functions were influenced by dark and light cycling and had plasticity related to retinal stimulation.[18]

Reductions in acuity have been reported secondary to cannabis consumption.[19] Adams and colleagues did not find reductions in static acuity but did find reductions in dynamic acuity after cannabis consumption.[20] The structural findings related to the cones in the retina and koniocellular layers of the LGN offer an explanation for the functional findings of color impairment with cannabis consumption. Several researcher have identified color deficits along the blue axis. Adams and colleagues found dose-related impairment with the consumption of cannabis was identified using the Farnsworth-Munsell 100 hue test and the findings were along the blue axis. The deficits were similar to those blue deficits that occur with retinal based pathology leading researchers to conclude that the origin of the dysfunction was in the retina itself.[21] Dawson and colleagues supported the findings of significantly reduced color vision functions with decreased color matches among those having consumed cannabis.[19] In studies of retinal tissue in vitro; Hu and
colleagues found evidence of cannabinoid function in postsynaptic cone bipolar cells that interact with cone photoreceptors providing further physiologic evidence to support the functional deficits in color processing.[12]

There is evidence of dysfunction related to dark adaptation, light adaptation, glare recovery and photopic functions with the consumption of cannabis.[19, 22] This may be related to changes in pupil function, suppression of central inhibitory or excitatory retinal functions, abnormal retinal functions peripherally or any combination. The dysfunctions persist for two hours after cannabis consumption. That cannabis impacts central photopic-based functions is evidenced by studies that demonstrate an increase in scotopic functions. There are reports of improved night vision with the use of cannabis.[23] In support of increased peripheral scotopic function is the discovery of a novel exogenous cannabinoid in rod segments and elsewhere in the central nervous system of a primate model, GPR55.[24]

The changes to scotopic and photopic functions may be caused by an imbalance of dopamine and melanopsin within the retina that is caused by cannabis consumption. Cannabis suppresses dopamine throughout the body, including the retina.[5] This has significant implications for visual functioning as dopamine is abundant in the retina and necessary for the signaling related to modulation functions within the retina, such as temporal and spatial processing as well as fine acuity. A recent study demonstrated that early age and long-term use of cannabis results in reductions of these functions.[25] Chronic users who had started consuming cannabis at a younger age showed reductions in low spatial frequency contrast sensitivity functions. Brain imaging has demonstrated permanent structural changes in the precuneus, a visually-related brain region involving integration of signals, of early age long term cannabis consumers and this supports the findings of functional reductions in the visual system that rely on input from multiple sensory signals.[26] A primate model has demonstrated that dopamine is necessary for contrast detection and in particular with lower light levels.[27] A depletion model for dopamine in a rodent also demonstrated that dopamine is crucial for contrast detection functions.[28] Another rodent model demonstrated significant deficits in visual and non-visual retinal functioning if the dopamine levels are disrupted during developmental periods.[29] In humans, the use of cannabis during adolescence has been demonstrated to be damaging to numerous cognitive processes including those involved in vision. Both the primate and rodent models further demonstrated dopamine’s involvement in non-visual functions such as circadian and basic light responses such pupillary functions.

Motion perception is changed with cannabis use. The detection of coherent motion is significantly reduced in long term, but abstinent at the time of testing chronic cannabis users. [30] When cannabis is used prenatally the exposed children have been found to have changes in global motion perception, with a significantly greater ability to detect global motion compared to children not exposed prenatally.[31] This may seem to be a positive outcome. It is important to consider the overall implications of this. Children prenatally exposed to cannabis have been found to suffer learning and memory deficits with an increase in impulsivity.[32] A group of adolescents who had been exposed to cannabis prenatally were found to have alterations in visuospatial working memory when assessed using functional magnetic resonance imaging.[33] Chronic long term, but abstinent adult cannabis users have attention and memory dysfunctions. In functional magnetic resonance imaging studies multiple regions of the brain were shown to be changed. Many of the regions demonstrating change are involved in visual processing.[34]

**Cannabinoids/Cannabis and Ocular Structural and Photic Non-visual Functioning**

Early reports in the 1970s indicated that marijuana impacted pupillary function with dose-related constrictions of the pupil.[18, 19] More recent reports using pupillometer technology are documenting dose-related dilations of the pupil.[20, 21] Dilated pupils as well as a slow pupil reaction were reported to be indicators of cannabis consumption by Bramness and colleagues. The diminished pupil reaction persisted for the first two hours. They observed an increase in dilation among those with blood-cannabis concentrations above 2.9 ng/ml, but the observation was only present in 35% of those consuming cannabis.[22]

Despite the conflicting reports in the literature, clearly the use of cannabis and cannabinoids impact anterior chamber function and this includes pupil, trabecular structures and ciliary body. The functional changes in the ciliary body are most likely contributing to the reductions in intraocular pressure (IOP) that historically have been reported in the literature.[35]
The reports regarding ocular motility are varied. While brain regions that involve eye movement are clearly impacted by cannabis, how the functional movements are affected is less clear. Application of eye movement as an indicator of impairment for cannabis use is inconclusive. In a study reported in 2012 with the cooperation of law enforcement, 25 cannabis-using participants identified by urinalysis to have cannabis as the only intoxicant, found lack of evidence for deficits in eye movements.[36] The study relied on opportunistic participants who had consumed cannabis/marijuana and there were no controls available for dosing. A study undertaken in the 1970s found deficits in horizontal gaze nystagmus (HGN) as well as tracking with the consumption of cannabis, but not as significant as compared to the intoxication with alcohol.[20] The percent of THC in the government-produced marijuana product used for testing was reported to be between 1.4 and 2.2%. Smooth tracking and saccadic tracking are reduced with alcohol but not with marijuana or a placebo in the motion study.[37] This study also used a government-produced product with a THC below 4.0%. In a study of 20 adults using cannabis and cannabis combined with alcohol researchers found that with cannabis alone the users showed impairment with the field sobriety test of one leg stand, but dysfunctions in regards to HGN were when cannabis was combined with alcohol.[38] This study was conducted in Holland and used a product that contained 11% THC. This was considered to be the average potency of recreational and medicinal marijuana/cannabis in Holland. Recent studies comparing plant cannabis and the use of synthetic cannabis demonstrate a high rate of HGN among those using synthetic cannabis compared to those using plant cannabis. The rate of HGN was 50% in the synthetic group with 12% in the plant group.[39]

A confounder in the few early human marijuana studies as well as the more contemporary research is the standardization of marijuana/cannabis dosing. Government funded research in the United States utilizes a standard marijuana product that is produced on a single farm in Mississippi. The plant strain was developed in the 1970s and is the product that was used and still is used to conduct medical research related to cannabis/marijuana when funded by the United States government. This marijuana product has a THC that is generally below 5.0%. The percent THC in marijuana and cannabis products has increased considerably. A study analyzing the levels of THC in confiscated marijuana/cannabis in the United States found that the average percent went from 3.4% in 1993 to 8.8% in 2008.[40] Current marijuana products can have as high as 30% with non plant forms such as oils and dabs having the potential to be as high as 80% THC.[41]

Approved Ocular Use: Medicinal Cannabis for the Treatment of Glaucoma

The use of smoked cannabis was first reported to decrease IOP in 1971.[42] However, there are risks associated with using marijuana/cannabis to treat glaucoma and the dosing required to maintain an adequate reduction of IOP would most likely interfere with quality of life. The American Academy of Ophthalmology took a formal position on treatment of glaucoma with cannabis in 1999, “The Academy Task Force on Complementary Therapies believes ...no scientific evidence has been found that demonstrates increased benefits and/or diminished risks of marijuana use to treat glaucoma compared with the wide variety of pharmaceutical agents now available. These agents include ..(drugs) as well as surgical treatments......” They affirmed their position in 2013 and again in 2014 citing additional evidence, "Based on reviews by the National Eye Institute (NEI), the Institute of Medicine (IOM), and on available scientific evidence, the American Academy of Ophthalmology Complementary Therapy Task Force finds no scientific evidence demonstrating increased benefit and/or diminished risk of marijuana use in the treatment of glaucoma compared with the wide variety of pharmaceutical agents now available. Potentially serious side effects associated with smoking marijuana include an increased heart rate and a decrease in blood pressure. Studies of single-administration marijuana use have shown a lowering of blood pressure concurrent with the lowering of IOP. This raises concerns that there may be compromised blood flow to the optic nerve, but no data have been published on the long-term systemic and ocular effects from the use of marijuana by patients with glaucoma."[43] The American Glaucoma Society does not support use of cannabis for the treatment of glaucoma and offered their position in 2009. “The mainstay of treatment for glaucoma patients is lowering the IOP [intraocular pressure]... Although marijuana can lower the intraocular pressure (IOP), its side effects and short duration of action, coupled with a lack of evidence that it use alters the course of glaucoma, preclude recommending this drug in any form for the treatment of glaucoma at the present time."[44]

While there are concerns about cannabis and the smoking of cannabis as a treatment, there are indications that isolated cannabinoids and synthetic cannabinoids may be useful treatments. Regarding plant derived cannabis, studies
have shown that marijuana and Δ9-THC can lower IOP when administered orally, intravenously, or by smoking.[42][45] One early study demonstrated a lowering of IOP that was sustainable and lasted up to four hours but utilized the consumption of cannabis in smoked form at the rate of up to 15 smoked joints per day.[46] Early studies showed cannabis to lower IOP by approximately 25% in 60 to 65% of both glaucoma and non-glaucoma patients. [42, 47]

There is evidence that the blood-pressure lowering effect of marijuana mediates the temporary reduction in IOP. The concern is that this also reduces perfusion at the optic nerve.[47] Another theoretical mechanism for the Δ9-THC lowering effect on IOP is action on ciliary body cannabinoid receptors and lowering aqueous humor production.[35, 48] As an indication that treatment of plant cannabis in its current state is less than an ideal treatment for glaucoma a study comparing the endogenous cannabinoid AEA to bimatoprost demonstrated a greater efficacy to produce ciliary body action occurred with the bimatoprost.[49]

Synthetic cannabinoids are currently under study for the treatment of glaucoma. The synthetic cannabinoid WIN55212-2 decreases the IOP in human glaucoma resistant to conventional therapies.[35] A surgically induced rodent glaucoma model using the synthetic cannabinoid WIN55212-2, administered topically three showed a rapid decrease in IOP by as much as 47% in treated animals with no significant cardiovascular effects or ocular toxicity were noted during chronic topical therapy with either drug or vehicle.[50] This study found that there were no significant cardiovascular effects or ocular toxicity associated with the chronic topical therapy.

The same synthetic cannabinoid in a primate monkey model showed an 18% reduction in the production of aqueous humour without changes in the trabecular outflow facility. There was a greater IOP lowering indicating additional mechanisms must also be involved such as the ciliary action.[48] A model using plant cannabis versus an isolated cannabinoid showed that the absolute change in IOP had a dose-response relationship, with an increasing dose associated with greater reduction in IOP from baseline. The effect lasted only 3 to 4 hours.[51] The topical application of the CB2 receptor agonist JWH-133 used in in vivo experiments on a rabbit model, did not have any effect on IOP compared to vehicle treatments. This indicates that the CB2 receptor agonists may not be involved in the regulation of IOP.[52]

**Neuroprotection and Anti-inflammatory**

The CB2 receptors are known to be involved in anti-inflammatory processes[53] and are potentially neuroprotective.[54] The CB1 receptors may also play a role. In a N-methyl-D-aspartate stress glaucoma model it was demonstrated that cannabinoids played a neuroprotective role related to retinal ganglion cell death.[55] The synthetic cannabinoid WIN 55212-2 demonstrated a neuroprotective effect on retinal ganglion cells using an ischemia-induced IOP model. The CB1 populations were involved.[56] The non-psychoactive cannabinoids are thought to have the role as anti-inflammatory. This has been demonstrated in the retina. A rodent model indicated that cannabidols reduced neurotoxicity, inflammation and the blood-retinal barrier breakdown in a model of diabetic retinopathy.[57]

The endogenous human cannabinoid, anandamide (AEA) has been demonstrated to play an anti-inflammatory role related to Muller glia [58] and this was demonstrated in retinitis secondary to HIV.[59]

**Conclusion**

Cannabis impacts the functions and structures in the visual system. Plant-based cannabis in the form of consumed marijuana is complex and contains multiple cannabinoids. The cannabinoid THC with its psychotropic attributes is of particular concern. There are specific concerns regarding the impact of THC on prenatal development, development in adolescence and the long-term consequences in neuroprocessing throughout the lifespan. Currently, plant-based use of cannabis for the treatment of glaucoma is far inferior to conventional treatments. However, that does not mean that further study and development are not warranted. Further research is indicated in order to maximize the the therapeutic potentials related to cannabis and cannabinoids. Alternatives to consumption of cannabis in plant form are necessary in order to minimize the negative consequences of daily use and detriments to quality of life.
The primary care clinician needs to be aware of the effects the consumption of cannabis has on their patients. It is critical to determine if cannabis is being used in any form, either medicinal or recreational. Further, an understanding of the type cannabis product being consumed is necessary in order to determine its impact on the visual system. In addition to the cognitive dysfunctions that cannabis may induce within the visual neuroprocessing systems are the implications for interactions with other ocular treatments such IOP lowering medications. The example of a patient with existing visual field loss and borderline pressures comes to mind. Such a patient may be hampering the achievement of an ideal target IOP and decreasing their safety when driving when using cannabis.

While cannabis should not be considered as a treatment of choice for glaucoma, that does not rule out cannabis as viable treatment for other medical ailments. Knowing the percentage of THC, route of consumption and the presence of other cannabinoids can influence discussions regarding prudent use for medicinal purposes. Optometric clinicians often provide care for those patients that have the diseases for which medical cannabis is approved. In many of these diseases the visual system may already be impacted due to the underlying pathology. Examples are; Multiple Sclerosis, HIV, Parkinson’s disease and Alzheimer’s disease.

There is much research to be done before we can fully embrace cannabis as a treatment for ocular disease. However, that does not mean that optometrists should not play a critical role in the management of patients using cannabis either recreationally or medicinally.


4. Substance Abuse and Mental Health Services Administration: **Results from the 2013 National Survey on Drug Use and Health: summary of national findings.** HHS Publication No (SMA) 14-4887 NSDUH Series H-49


25. Mikulskaya E, Martin F: *Contrast sensitivity is impaired at low spatial frequencies in early-onset cannabis users in low light conditions.* School of Psychology, University of Newcastle 2015.


34. Chang L, Yakupov R, Cloak C, Ernst T: Marijuana use is associated with a reorganized visual-attention network and cerebellar hypoactivation. Brain 2006 May;129(Pt 5):1096-112 Epub 2006 Apr 3.


Questions

1. Research indicates there are no reasonable expectations that cannabinoids will be useful for treatments related to treating inflammation in the eye.

   True
   False

2. There are an estimated ______________ in California holding medical marijuana registrations, allowing for legal medical use of marijuana.

   A. 25,000
   B. 50,000
   C. 75,000
   D. 100,000
   E. 125,000

3. Cannabis and the cannabinoids related to IOP lowering have which of the following cannabinoid demonstrating animal models of IOP reduction.

   A. WIID5521-2
   B. WIN2166-2
   C. WIID2166-2
   D. WIN5521-2
   E. WINR12D-2

4. In a study comparing current approved glaucoma drug therapies to the endogenous cannabinoid AED, which was demonstrated to superior in ciliary action induction.

   A. Bimatoprost
   B. Latanoprost
   C. Travoprost
   D. PGF2alpha

5. The American Glaucoma Society takes the position:

   A. Cannabis is viable treatment for glaucoma under the supervision of a medical eye care provider.
   B. Cannabis is as effective, if not superior to current treatments.
   C. Cannabis should be used as an adjunct to current therapies.
   D. Cannabis lowers IOP effectively and should be used in isolation, instead of current therapies.
   E. Cannabis with its short duration and side effects, precludes its use as a treatment.

6. In humans there are thought to be two primary endogenous compounds acting on cannabinoid receptors. They are:

   A. N-arachidonylethanoalmine (Anandamide, AEA) and 2-arachidonoylglycerol (2-AG)
   B. 2-arachidonoylglycerol (2-AG) and Melanopsin
   C. N-arachidonylethanoalmine (Anandamide, AEA) and Melanopsin
   D. N-arachidonylethanoalmine (Anandamide, AEA) and Dopamine
7. The changes in blood pressure related to cannabis consumption are hypothesized to negate some of the benefit of decreased IOP with cannabis consumption. This is due to:

A. Increases in blood pressure create greater impedance to circulating blood in retinal vasculature.
B. Decreases in blood pressure change the anterior chamber dynamics creating an increase in production of aqueous humor.
C. Decreases in blood pressure changes the perfusion across the optic nerve.
D. Increases in blood pressure coupled with a decrease in heart rate impacts ciliary body response.

8. Which is an accurate statement for the distribution of cannabinoid receptors in the retina:

A. Cannabinoid receptors are located only in cones, and are not distributed in rods.
B. Cannabinoid receptors are isolated in location only in the RPE.
C. Cannabinoid receptors are not located in the retina at all.
D. Cannabinoid receptors are located throughout the retina.

9. The use of eye movements and nystagmus are conclusive evidence of impairment secondary to cannabis use.

True
False

10. Cannabis recreational use is considered to be minimal with few users.

True
False
Please fill out this form completely. Mail or fax (along with payment) to:

Mail:
COA – Education Coordinator
2415 K Street
Sacramento, CA 95816
Fax: 916-448-1423

RECEIVING YOUR TRANSCRIPT

Name: _________________________________
License Number: _________________________
Phone Number: _________________________

☐ Please check here if you would like to receive your transcript via MAIL.

Mailing Address:
_____________________________________
_____________________________________
_____________________________________

☐ Please check here if you would like to receive your transcript via E-MAIL.

E-mail Address
_____________________________________

PAYMENT INFORMATION

☐ COA Member - $15

☐ Non-Member - $35

☐ Check or Money Order enclosed (payable to the California Optometric Association)

☐ Credit Card: ☐ VISA ☐ MC ☐ AMEX
Card Number: ________________________________ Expiration Date: ______________

CCV#: ___________ (VISA & MC – 3 digit # on back; AMEX – 4 digit # on front)

Name on Card: ____________________________________

Authorized Signature: ______________________________

FOR OFFICE USE ONLY

<table>
<thead>
<tr>
<th>Date Received</th>
<th>Invoice Batch</th>
<th>ID Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>