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ABSTRACT & COMMENTARY

Kratom Alert: FDA Concerns

By David Kiefer, MD

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Dr. Kiefer reports no financial relationships relevant to this field of study.

SYNOPSIS: Kratom, a plant that is banned in some countries, is available in the United States and has some safety concerns, mostly related to its opioid-like effects.

SOURCE: FDA Statement. Statement from FDA Commissioner Scott Gottlieb, M.D. on FDA advisory about deadly risks associated with kratom. Nov. 17, 2017. Available at: http://bit.ly/2hq3sTF. Accessed Jan. 7, 2018.

This Abstract & Commentary is drawn from an FDA press release, differing from the usual focus on randomized, controlled trials. The primary reason for this is to highlight an important safety concern, and weave in some of the recent background research relevant to this natural product.

Kratom (*Mitragyna speciosa*, Family Rubiaceae) is a tree found in Southeast Asia and Africa, and its leaves are used medicinally, usually as a tea, for several health conditions.[1] In the United States, it is marketed as a safe natural substance for the treatment of pain, anxiety, and depression. As per the FDA press release, there is concern about the self-treatment of these serious conditions, but also the fact that kratom appears to produce opioid-like effects and the expected associated issues of addiction, withdrawal, and death; 36 deaths have been reported. Outside the supervision of a licensed healthcare provider, kratom also is used to treat opioid withdrawal, another FDA concern. There has been a marked increase in calls made to U.S. poison control centers about the use of kratom-containing products.

At the end of the press release, the FDA director reminded the scientific community and the public at large about the process that exists for drug applications and the evaluation of dietary supplements, a path that he recommended for kratom or any other substance touted to be part of the solution to the opioid epidemic. The FDA considers kratom to be an unapproved drug and has "taken action against

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kratom-containing dietary supplements." Officials are seizing the shipments and destroying the product, as the FDA continues the process of investigating the safety and efficacy of this botanical medicine.

■ COMMENTARY

Not all plants or natural products are safe. Kratom is one plant that may fall into this category, but the story is more complicated. Kratom contains more than 40 phytochemicals in the class of indole alkaloids, the primary one mitragynine, although 7-hydroxymitragynine also is mentioned commonly in the literature.[1-3] The content of the alkaloids varies depending on geographic location, plant age, and numerous other factors affecting the physiological effect of the plant. Storage also may play a role; mitragynine may be converted to 7-hydroxymitragynine upon exposure to air.[3]

An additional layer of complexity stems from the effect of kratom on opioid receptors. At the mu-opioid receptor, kratom extracts show both agonist (mitragynine) and antagonist (other alkaloids) activity.[1,2] Kratom extracts appear to be weak competitive antagonists at kappa-opioid receptors and weak antagonists at delta-opioid receptors, although extrapolating from some of this animal research to human effects is difficult and still needed.[1,3] Mitragynine also may bind to other central nervous system receptors, including alpha-2-adrenergic, adenosine, serotonin, and dopamine.[1] Much of the differential receptor binding is thought to be dose dependent, with opioid effects occurring at higher dose ranges. It is thought that the opioid effects of mitragynine are 13 times more potent than morphine, and those of 7-hydroxymitragynine are even more potent.[4]

Most people use kratom in a dose less than 8 grams per dose, delivering 120-180 milligrams of mitragynine.[1] It is thought that a stimulant effect may occur in doses of 1-5 grams, with more opioid-like effects occurring at or above 8 grams.[1-3] These latter effects are where kratom has been used for opioid withdrawal symptoms. Adverse effects have been documented. Fatalities have occurred with the use of a product called Krypton, a blend of mitragynine and O-desmethyltramadol, although it is unknown which of the compounds ultimately caused the deaths.[2] Other adverse effects include hypertension, cognitive changes, dependency, and several cardiovascular and gastrointestinal system effects.[4] Kratom overdose has been described and may be associated with seizures. A withdrawal phenomenon, not unlike opioid withdrawal, also is seen.[4]

As some experts have mentioned, there is potential for kratom to play a role in the opioid epidemic, but much scientific work remains to arrive at a consistent recommendation about safety and efficacy.[3] More human clinical trials are necessary as are basic pharmacokinetics. Does basic science research on animals extrapolate to humans? Quality control and product labeling seem to be important given the phytochemical variations that have been documented, and they could affect the physiological effects of kratom significantly. This latter issue is not unlike challenges facing many other herbal products — one of the reasons for the development of such initiatives as the Botanical Adulterants Program through the American Botanical Council and the widespread use of third-party certification programs. Is the FDA approach of product seizure and action against kratom-containing dietary supplements justified? Clinicians are comfortable with a "do no harm" approach to patient care, so perhaps for now, as some of the basic pharmacokinetics and clinical effects are clarified, a "use no kratom" strategy seems warranted. ■

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ABSTRACT & COMMENTARY

A Closer Look at the Effects of NSAIDs on Blood Pressure

By Michael H. Crawford, MD

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Dr. Crawford reports no financial relationships relevant to this field of study.

SYNOPSIS: An ambulatory blood pressure monitoring substudy of the PRECISION trial showed that ibuprofen use significantly increased mean 24-hour systolic blood pressure compared to celecoxib. Further, naproxen produced intermediate results despite equivalent pain relief in patients with arthritis.

SOURCES: Ruschitzka F, Borer JS, Krum H, et al. Differential blood pressure effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: The PRECISION-ABPM (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement) trial. *Eur Heart J* 2017;38:3282-3292.

Weintraub WS. Safety of non-steroidal anti-inflammatory drugs. *Eur Heart J* 2017;38:3293-3295.

Selective and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are used often and on a regular basis in osteoarthritis patients, many of whom present with concomitant hypertension. However, the relative effect of various agents on blood pressure (BP) is unclear. Thus, the ambulatory blood pressure measurements (ABPM) substudy of the Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen (PRECISION) study of patients with osteoarthritis with or at increased risk of cardiovascular (CV) disease is of interest. Patients were randomized to three NSAIDs at a low dose that could be increased as needed (celecoxib 100-200 mg twice per day vs. ibuprofen 600-800 mg three times per day vs. naproxen 375-500 twice per day). ABPMs were performed every 20 minutes during awake times and every 30 minutes during sleep times. The primary endpoint was the change from baseline in mean systolic BP (SBP) at four months. Also, the relationship between the change in BP and subsequent major CV events were analyzed. Successful completion of the study was accomplished in 374 of the 545 subjects enrolled at 60 centers in the United States. The change in mean SBP was significant for ibuprofen (3.7 mmHg; $P < 0.001$) but not for celecoxib (-0.3 mmHg) or naproxen (1.6 mmHg). Clinic SBP showed similar results (5.2 mmHg with ibuprofen, 1.0 mmHg with celecoxib, and 3.2 mmHg with naproxen). During the 2.5-year follow-up, few patients experienced major CV events (nine with ibuprofen, seven with celecoxib, and six with naproxen). The authors concluded that the nonselective NSAID ibuprofen compared to the selective NSAID celecoxib showed a significant increase in mean SBP on ABPM.

■ COMMENTARY

Celecoxib is the only selective COX-2 inhibitor left on the market in most of the world. Thus, it was reassuring to see in the full PRECISION trial that hard CV endpoints were not significantly different with celecoxib compared to ibuprofen or naproxen (2.3% vs. 2.7% vs. 2.5%, respectively). Also, there were no differences in arthritis quality-of-life measures, but there were less observed gastrointestinal and renal adverse effects with celecoxib. It is well known that NSAIDs can increase BP. Small increases in SBP can increase the likelihood of adverse CV events significantly. Indeed, the observed adverse CV effects of NSAIDs may be more due to BP changes than their effect on endothelial function. Hence, this substudy of PRECISION patients undergoing ABPM is pertinent. PRECISION-ABPM demonstrated several important points. Mean SBP/24 hours was increased only by the nonselective NSAIDs. Also, hospitalizations for hypertension were 69% higher for patients on ibuprofen than those on celecoxib. Among subjects with normal BP at baseline, new hypertension was diagnosed in 10% on celecoxib, 23% on ibuprofen, and 19% on naproxen. The odds ratio for new hypertension on celecoxib was 0.39 ($P = 0.004$). These results were consistent across all subgroups, including factors such as race, diabetes, chronic kidney disease, and aspirin use. This more favorable effect on BP was accomplished at equivalent efficacy with arthritis relief. The major limitation of this study was that the FDA limited the dose of celecoxib that could be used to a maximum of 400 mg/day. Most patients were on 200 mg/day. Previous studies that used higher doses showed increased CV adverse events with celecoxib vs. placebo. Also, there was no placebo group in PRECISION, although it would have been difficult to conduct such a study in patients with symptomatic arthritis. However, the study was blinded and randomized. It is reassuring that low-dose celecoxib is reasonably safe. However, it is not completely safe, as a COX-2 inhibitor reduces prostacyclin and increases thrombosis risks. Finally, the results of PRECISION cannot be extrapolated to intermittent use of these drugs for arthritis flares. ■

ABSTRACT & COMMENTARY

Functional Imaging Studies in Parkinson's Disease

By Harini Sarva, MD

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Dr. Sarva reports no financial relationships relevant to this field of study.

SYNOPSIS: A meta-analysis of 142 studies demonstrated that functional imaging studies in Parkinson's disease using tracers for aromatic acid decarboxylase showed smaller defects compared to those using tracers targeting dopamine transport and VMAT2. Symptom severity correlated linearly with dopamine neuron loss as determined by these imaging studies.

SOURCE: Kaasinen V, Vahlberg T. Striatal dopamine in Parkinson disease: A meta-analysis of imaging studies. *Ann Neurol* 2017;82:873-882.

Kaasinen et al assessed 1,520 papers obtained through a PubMed search using various search terms, including dopamine, Parkinson's disease (PD), parkinsonism, PET, and SPECT. Out of these 1,520 papers, 142 studies were included in this analysis if they met the following inclusion criteria: human PET or SPECT study; aromatic l-amino decarboxylase (AADC), vesicular monoamine transporter 2 (VMAT2), or dopamine transporter (DAT) tracer was used; idiopathic PD patients were compared with healthy controls; and binding was reported as a mean for both PD and healthy controls in at least one striatal region. Twelve studies were excluded because of repetition of subjects. There were 157 separate PD samples in these 142 studies. The total PD patients was 3,605 and the total healthy controls was 2,352. Of these 142 studies, 67 were AADC studies, 64 were DAT studies, and 11 were VMAT2 studies. All the studies demonstrated a 13.2-77% lower binding of AADC, DAT, and VMAT2 in PD patients compared with controls. In order of effect size from most to least, the posterior putamen showed the most effect size, then the entire putamen, followed by the anterior putamen, and lastly the caudate nucleus. The defect in AADC was consistently smaller than the defects in VMAT2 or DAT. The correlation between disease severity and dopamine loss was linear. This correlation was strongest in the caudate compared to the putamen. The longitudinal studies (total of 18; 3 AADC studies, and 15 DAT studies) demonstrated inconsistent results but suggested a negative exponential progression of dopamine loss.

■ COMMENTARY

Dopaminergic functional imaging has been used in research for nearly 30 years. This study confirms the relationship between dopamine loss and disease severity. The strengths of this meta-analysis include the large number of studies and subjects. Publication bias was not found to be significant. However, important considerations must be noted. Different methods and machines can provide varying results that can contribute to the stark contrast between neuropathology showing a lack of dopamine fibers and imaging, which shows a reduction in fibers by 50%. In addition, PD has varying subtypes that also may contribute to the large range in reduction in binding of AADC, VMAT2, and DAT. Along these lines, the search terms included atypical parkinsonisms, and these imaging modalities cannot accurately distinguish between PD and the atypical Parkinson patients. Thus, the inclusion of atypicals in these studies can lead to varying binding reduction. Although the imaging modalities can help correlate disease severity and neuronal loss at a single point, longitudinal analysis was found to be inconsistent. Thus, these functional imaging studies still are not reliable biomarkers of PD. Further research into the type of tracer and target is required to establish functional imaging as a reliable biomarker. ■

ABSTRACT & COMMENTARY

Updated Recommendations for Prevention of Hepatitis B Virus Infection

By Stan Deresinski, MD, FACP, FIDSA

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Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: Fresh recommendations for prevention of hepatitis B virus infection focus on testing and management of newborns.

SOURCE: Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep* 2018;67(No. RR-1):1–31.

As part of its commitment to eradicate hepatitis B virus (HBV) infection in the United States, the CDC has published an update of recommendations for the prevention of HBV infection by the Advisory Committee on Immunization Practices. The first two elements of the overall strategy have been routine HBsAg testing of all pregnant women and vaccination and hepatitis B immune globulin (HBIG) administration in the United States of all infants born to antigenemic mothers, as well as vaccination of all other infants shortly after birth. The third and fourth elements are vaccination of all previously unvaccinated children and adolescents, together with routine testing of at-risk adults.

The updated recommendations include the following: All pregnant women found to be HBsAg positive should undergo testing for HBV DNA, which allows identification of infants at the greatest risk of infection. The recommendations note evidence that antiviral therapy during pregnancy reduces the risk of transmission and point out that the American Association for the Study of Liver Diseases recommends treatment, preferably with tenofovir, of the mother if her HBV DNA level in plasma is > 200,000 IU/mL. All infants born to mothers for whom the results of testing during pregnancy are not known, but who have exhibited prior evidence of HBV infection, should be treated as if born to antigenemic mothers.

Many new recommendations concern the management of newborns and include the following. All clinically stable infants with a birth weight > 2,000 grams born to antigen-negative mothers should receive their first dose of vaccine within 24 hours of birth. Vaccinated infants born to mothers whose antigen status remains unknown should be tested for the presence of a protective anti-HBs level at 9-12 months of age. All vaccinated antigen-negative infants with anti-HBs levels < 10 IU/mL should receive another dose of vaccine and undergo repeat anti-HBs antibody testing 1-2 months later. The originating institution, upon transferring the infant to another facility, should communicate its status of vaccination and HBIG receipt.

The following unvaccinated adults have been added to those previously considered at high risk of HBV infection and who should be vaccinated: travelers to endemic countries with population HBsAg prevalences > 2%; HCV-infected individuals; individuals with chronic liver disease; HIV-infected individuals; incarcerated individuals; anyone who desires vaccination, even in the absence of acknowledgement of specific risk.

All newborns weighing < 2,000 grams at birth should receive a vaccine and HBIG within 12 hours of birth, regardless of knowledge of the HBsAg status of the mother. If it proves not possible to determine the mother's status, the vaccine schedule should be completed as if the mother were antigenemic. In addition, they should undergo anti-HBs at 9-12 months and, if the serum level is < 10 IU/mL, should undergo revaccination.

■ COMMENTARY

The incidence of newly reported cases of HBV infection since vaccination was first recommended has decreased from 9.6 cases per 100,000 population in 1982 to 1.1 per 100,000 in 2015, an 85% reduction. Taking into account lack of diagnosis and underreporting, it is estimated that there were 21,900 new cases in 2015. Despite the overall decrease, there was a 114% increase in 2009-2013 in combined data from Kentucky, Tennessee, and West Virginia, which has been attributed to increasing injection drug use.

In contrast to acute infections, 95% of chronic HBV infections occur in those who are foreign-born, approximately 3.5% of whom are infected. Thus, while there has been remarkable progress toward the elimination of HBV infection in the United States, much work remains. ■

PHARMACOLOGY UPDATE

Ozenoxacin Cream 1% (Xepi)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a new antimicrobial for the topical treatment of impetigo. Ozenoxacin is a nonfluorinated quinolone antimicrobial with bactericidal activity against *Staphylococcus aureus* and *Streptococcus pyogenes*, as well as activity against methicillin-resistant *S. aureus*.[1,2] It is marketed as Xepi.

INDICATIONS

Ozenoxacin is indicated for the topical treatment of impetigo due to *S. aureus* and *S. pyogenes* in adult patients and pediatric patients ≥ 2 months of age.[1]

DOSAGE

Apply a thin layer topically to the affected area twice daily for five days.[1] The affected area may be up to 100 cm^2 or 2% of the total body surface area but not in excess of 100 cm^2 in pediatric patients.[1] The treated area may be covered with a sterile bandage or gauze dressing. Ozenoxacin is available as a 1% cream (10 g, 30 g, and 45 g tubes).

POTENTIAL ADVANTAGES

Ozenoxacin offers a new topical antimicrobial from a different pharmacologic class for impetigo.

POTENTIAL DISADVANTAGES

The drug is more effective than placebo; however, in the clinical trials, a significant percentage of subjects (44% and 63%) were considered clinical failures.[1]

COMMENTS

The approval of ozenoxacin was based on two Phase III studies.[1,3] Subjects with impetigo affecting up to 100 cm^2 and not exceeding 2% of body surface and ≤ 11 years of age were randomized to ozenoxacin or placebo. Both were applied twice daily for five days. Subjects with preexisting eczematous dermatitis or clinical evidence of secondary infections were excluded.

Overall clinical success was defined as no need for additional antimicrobial therapy on the baseline affected area and absence/reduction in clinical signs and symptoms at the end of therapy (days 6-7). This varied slightly between studies. Study 1 assessed the absence of exudate/pus, crusting, tissue warmth, and pain, as well as erythema/inflammation, tissue edema, and itching as less than mild. In Study 2, endpoints were absence of blistering, exudates/pus, crusting, and itching/pain, and mild or improved erythema/inflammation.

Clinical successes were 34.8% vs. 19.2% in Study 1 and 54.4% vs. 37.9% in Study 2. In the subjects with the most frequently identified bacteria (*S. aureus* and *S. pyogenes*), clinical successes were 38% vs. 16% and 40% vs. 10% in Study 1 and 57% vs. 33% and 79% vs. 40% in Study 2. There is negligible systemic absorption of ozenoxacin when up to 1 g was applied to up to 200 cm^2 of surface area on intact or abrade skin.[1]

CLINICAL IMPLICATIONS

Impetigo is a common bacterial skin infection, particularly in children 2-5 years of age.[4] The most common type is nonbullous (70%) caused by *S. aureus* or *S. pyogenes*. The less common (30%) bullous generally is caused by *S. aureus*. The Infectious Diseases Society of America recommends topical or oral therapy.[5]

Topical treatment includes either mupirocin or retapamulin twice daily for five days. Ozenoxacin may be another option and is at least as comparable to retapamulin.[2] The cost for ozenoxacin was not available at this time. ■

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Clinical Briefs

By Louis Kuritzky, MD

Addressing Insomnia

SOURCE: Buysse DJ, et al. *JAMA* 2017;318:1973-1974.

Everyone likely experiences transient sleeplessness sometimes. However, when sustained for at least three nights/week for at least three months (in the absence of factors that predictably would preclude normal sleep, such as excessive stimulants, illicit drugs, load ambient noise, prominent ambient light, restless legs syndrome), the condition merits the diagnosis of insomnia.

The potential consequences of insomnia are obvious even to those who experience an occasional transient sleep disruption: daytime fatigue and difficulty concentrating.

The American College of Physicians recommends cognitive behavioral therapy as preferred initial treatment for insomnia. When insomnia is a major component of depression, there is some advocacy for inclusion of soporific agents (e.g., zolpidem, zaleplon, eszopiclone) as "bridging" sleep agents during the initial titration of antidepressants, with discontinuation once antidepressants have established efficacy (assuming depression-related insomnia is resolving appropriately). Despite the entrenched habits of clinicians and patients for chronic use of sleep agents, evidence supporting this practice is weak. Clinical trials on which currently available sleep agents have been approved generally are short-term. The absence of long-term safety data is a cause for concern. It is suggested that when using soporific agents, short-acting agents are preferred (e.g., temazepam, zolpidem). If possible, intermittent use (three to four nights/week) also is preferred, with intention to taper and discontinue medications after three to four weeks. Ultimately, if cognitive behavioral therapy is insufficient to remedy insomnia, sedative-hypnotic agents must be added sometimes. Consultation with a sleep expert for refractory cases, or for cases requiring more sustained use of medications, is fully appropriate. ■

The Sticky Wicket of Androgen Receptor Modulators

SOURCE: Van Wagoner RM, et al. *JAMA* 2017;318:2004-2010.

For those of British or British Colonial heritage, "sticky wicket" probably needs no explanation, referring to the game of cricket as it does. In the United States, the term generally refers to croquet, so stated when a wicket is particularly difficult to pass through.

Enhancement of androgens in the United States is big business. But can consumers rely on internet-advertised products as safe, effective, and containing the stated constituents without adulterants? Van Wagoner et al obtained product samples (44 different products) of androgen receptor modulators sold online and analyzed their contents using the rigorous methods approved by the World Anti-Doping Agency.

Less than half the products tested contained the amount of active product claimed on the label. Almost 20% of the products contained none of the claimed active component. Some products contained substances banned by the World Anti-Doping Agency, and some contained growth hormone secretagogues.

Because many of these products are sold as dietary supplements, they are not subject to the same FDA regulations and surveillance as proprietary pharmaceutical drugs. Since many of the supplements contain substances that either have not been studied in humans or feature little safety data, clinicians should inform potential users about the limitations of such products. ■

Updated Hypertension Guidelines

SOURCE: Goldfarb IT. *JAMA* 2017;318: 2075-2076.

The most recent American Heart Association/American College of Cardiology (AHA/ACC) hypertension guidelines have created a literature stir, although there remain many clinicians who are not wholly on board with the updated recommendations. Since 1977, when the first National Heart, Lung, and Blood Institute-directed guidance on hypertension was issued, periodic updates have occurred. In 2013, responsibility for cardiovascular disease clinical practice guidelines was transferred to the AHA/ACC, which subsequently released this lengthy and detailed 2017 document.

Perhaps the most novel innovation is the recategorization of systolic blood pressure 130-139 mmHg or diastolic blood pressure 80-89 mmHg as stage 1 hypertension. Previously, this blood pressure zone was labeled prehypertension. The rationale for the new designation is, in part, that previous data indicated as much as a two-fold increase in cardiovascular disease risk when stage 1 hypertension is compared to blood pressure < 120/80 mmHg, coupled with convincing results from recent trials (e.g., SPRINT) that indicate systolic blood pressure levels < 120 mmHg are not only achievable — and, for the most part, safe — but also improve cardiovascular outcomes. Not all major agencies are advocates. For instance, the American Academy of Family Physicians (AAFP) has not endorsed the new guidelines, but instead advocates for the JNC 8 document, which the AAFP suggests provides a more robust evidence base. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. **Which of the following is *true* regarding kratom?**
   a. The root is used medicinally.
   b. At low doses, it appears to be an opioid-like analgesic.
   c. Adverse effects have been seen, often with opioid-like effects or withdrawal.
   d. The active compound mitragynine is often dosed at 1 to 2 milligrams.

2. **Which of the following is most likely to significantly elevate systolic blood pressure in patients with arthritis?**
   a. Celecoxib
   b. Ibuprofen
   c. Naproxen
   d. Acetaminophen

3. **Which of the following is *false* regarding the results of the study of functional imaging in Parkinson's disease?**
   a. Caudate had the most severe binding reduction.
   b. There were 11 VMAT2 studies.
   c. The correlation between disease severity and dopamine loss was strongest in the caudate nucleus.
   d. AADC binding defect was consistently smaller than the other two targets.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Physician Burnout:
A Multi-specialty Perspective

Type 2 Diabetes
Is Reversible