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Some Recent Issues: E-Cigarettes, Fecal Transplant, Bronchial Thermoplasty, Medical Marijuana

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"The best way to make your dreams come true is to wake up"

–Paul Valery

ABSTRACT

Recent updates in internal medicine include e-cigarettes for smoking cessation, fecal transplant for *Clostridium difficile* infection, bronchial thermoplasty for severe asthma and medical marijuana for several chronic disorders. Smoking is the leading preventable cause of disease in the world and efforts to find smoking cessation treatments has spearheaded the popularity of e-cigarettes that deliver nicotine in a more benign form than cigarettes. No robust scientific evidence is available regarding its efficacy and concern for abuse by minors is worrisome. *C. difficile* infection is the most common healthcare associated infection in the world that may be recurrent and severe. Fecal microbiota transplant is an effective and safe treatment for severe infection and can be performed in smaller medical centers with relative ease. Bronchial thermoplasty delivers thermal energy to the hypertrophied bronchial smooth muscle in chronic asthma patients to reduce its mass and contractility, thus causing long-term symptoms relief. Complications include bleeding, respiratory infections and pneumothorax, though it has been deemed a relatively safe procedure if done under the supervision of highly skilled physicians. Marijuana is an illegal recreational drug that has received recent attention for its potential medicinal properties. It may be effective in chronic diseases like, multiple sclerosis, chronic pain syndromes, amyotrophic lateral sclerosis, seizure disorders, wasting syndrome, and intractable nausea related to cancer and chemotherapy. Strict regulations have prohibited adequate scientific studies to prove its efficacy and vigorous research is ongoing as it is pronounced legal for medical use in many American states.

E-CIGARETTES FOR SMOKING CESSATION

Cigarette smoking remains the leading preventable cause of disease in the world with 6 million deaths globally, 400,000 deaths in USA, and 1 million deaths in India attributed to tobacco consumption costing approximately $ 300 billion every year.[1] Smoking causes 12 types of cancers as well as pulmonary disease, cardiovascular disease, peptic ulcers, and pregnancy complications. Secondhand smoke is carcinogenic as well. Thirdhand smoke, a recently recognized phenomenon, is the residue left behind after the cigarette smoke has disappeared that lingers on the walls, furniture, carpet, clothing, nails and hair. It combines with other indoor pollutants to form harmful chemicals that persist for years and are difficult to measure or eradicate. It can cause cancer and genetic disorders.

Smoking cessation needs to be addressed constantly by healthcare providers in a sustained effort to find ways to help smokers quit. **Current therapies include behavior modification strategies, nicotine replacement therapy, and pharmacological treatment like, bupropion and varenicline**, which are inconsistently effective. According to the Centers for Disease Control in the US, 70% smokers wanted to quit and 40% had made an attempt to quit in the past year using these techniques. A novel nicotine-dispensing device called electronic cigarette (EC) has gained popularity recently. It is a slimly built battery-operated tool that resembles a regular cigarette and dispenses nicotine to smokers in a form other than cigarettes. It contains nicotine mixed with different flavors and chemicals like, propylene glycol in a liquid form within a cartridge. The concoction is delivered to

the user through a heating device called the vaporizer, in a vapor form instead of smoke. On inhaling, the vaporizer is activated to deliver an aerosol of nicotine, unlike in a regular cigarette where nicotine is inhaled by burning tobacco leaves. Each cartridge can deliver 250–400 puffs equivalent to 1–2 packs of cigarettes. There are currently more than 450 varieties of EC in the market to choose from, some of them shaped like a pen, flash drive, or other commonly used item.

Almost half of all smokers in the US have tried EC and 4% use it on a regular basis. Supporters claim that smoke is more injurious than vapor since it contains toxins and carcinogens and therefore EC is safer. There is no robust data on whether EC is safe, effective, and appropriate as a smoking cessation device. A randomized clinical trial (RCT) showed 14% quit rate with e-cigarettes as compared to 4% with a nicotine free device.[2] Another RCT showed minor difference in quit rates between EC and nicotine patch or placebo device.[3] The major side effects of EC include dry cough, mouth and throat irritation, and lipoid pneumonia.[4]

Currently, there is no regulatory control over EC. There is a clear concern for minors using EC as they can obtain it easily from stores and online sales.[5] The fruity flavors mixed with nicotine as well as its ambiguous reputation attracts teenagers and young adults. They can be used without restrictions in smoke free zones like, schools and colleges. Young users of EC may "upgrade" to using regular cigarettes and nicotine may have a detrimental impact on the still-growing brains of adolescents. In pregnant women, nicotine can affect the fetal brain growth. EC may weaken the motivation of a serious smoker to completely quit smoking since while the mode of delivery may change, smokers continue their addiction to nicotine. Additional harms include toxic contaminants in the additives. Using EC may reduce cigarette smoking but not discontinue it entirely, resulting in concurrent use of both, a practice that could be a predictor of a longer duration of cigarette smoking. It is more harmful overall to have smoked *longer in time* than the *number* of cigarettes a day. These concerns violate the core messages about tobacco control, which are: "don't start" and "quit if you do". Long-term adverse effects are largely unknown and large robust clinical trials are needed to prove its efficacy.

FECAL MICROBIOTA TRANSPLANT FOR RECURRENT *CLOSTRIDIUM DIFFICILE* INFECTION

Clostridium difficile infection (CDI) **has surpassed methicillin resistant *Staphylococcus aureus* as the leading cause of healthcare associated infections in USA**, with an estimated annual cost of 1 billion dollars.[6] Up to 25% of patients with CDI will experience recurrence within 30–90 days, occasionally multiple recurrences.[6] Fecal microbiota transplant (FMT), first reported in 1958 for the treatment of *Pseudomembranous colitis*, is an effective, though cringe-inducing, treatment of recurrent CDI that involves the infusion of a fecal suspension from a healthy donor into the gut of a patient.

According to the **FMT workgroup guidelines published in 2011, the primary indications for FMT are**:

- Recurrent or relapsing CDI (three or more episodes of mild to moderate CDI and failure of a 6–8 weeks taper with vancomycin with or without an alternative antibiotic).
- Moderate CDI not responding to standard therapy (vancomycin) for at least a week.
- Severe or fulminant CDI with no response to standard therapy after 48 hours.[7]

The imbalance of commensal intestinal flora (also known as microbiota) is known as dysbiosis and can lead to recurrent CDI. These organisms help maintain a balanced and protective immunologic gut physiology. Antibiotics can breach this protective barrier and encourage colonization by *C. difficile.* It appears that abnormally low levels of intestinal *Bacteroides* and *Firmicutes* species may predispose a patient to recurrent CDI, although other organisms are likely involved.[6] As stool is biologically active, FMT from a healthy donor has been proven to correct dysbiosis, to restore the normal bacterial milieu, to eradicate *C. difficile*, and to prevent recurrence.[6]

In an RCT done in Amsterdam, patients with recurrent CDI were randomized to either FMT versus a standard 2-week treatment with vancomycin.[8] The former group had an 81% resolution with one infusion and 94% after a second infusion in those who had recurrence. In the latter group, only 31% in the vancomycin group ($p < 0.001$) had achieved resolution. Of note, a second randomized trial is ongoing. Another multicenter study designed for long-term follow-up revealed a primary cure rate of 91% and a secondary cure rate of 98% for a mean follow-up of 17 months.[9]

A fresh stool sample less than 6 hours old is recommended. In a blender provided by the patient, the donor stool is blended with nonbacteriostatic saline. After a proper slurry-like consistency is achieved, the mixture is filtered through gauze pads to remove particulate matter. The liquefied stool is then collected within 60 cc catheter tipped syringes. The stool is introduced into the recipient in either of two ways: (1) upper (gastrointestinal tract) GI tract via a nasogastric tube, and (2) lower GI tract via colonoscopy or retention enema. For colonoscopy, at least 50 grams is recommended and for upper GI tract administration, smaller amounts may be used. **All antibiotics must be stopped for 2 days before FMT and indefinitely after**.

Donors have to be carefully screened for transmissible infections such as, hepatitis B, C, HIV, syphilis, ova and parasites. **Exclusion criteria include: recent antibiotic use in the last 3 months,**

high-risk sexual behaviors, recent incarceration and body piercings/tattoos. Relative exclusion criteria include: history of inflammatory bowel disease, intestinal malignancy, and immunosuppression. These patients may have potential underlying dysbiosis.

The donor could be a close relative or an unknown volunteer: there is no significant difference in the resolution rates. It typically takes 5–7 days for donor testing to be completed at a cost of approximately $ 500. An alternative is to use a stool bank where volunteer donors may be reimbursed for their sample. Samples can be ordered for overnight delivery for urgent situations. Each frozen stool sample costs $ 250, and needs to be stored in a proper medical freezer prior to use.

Patient safety remains a concern, especially in the immunosuppressed though recent studies have shown that it may not be as dangerous as initially thought to be. Short-term adverse events include diarrhea, cramping, belching and constipation.[10] Rarely there may be a flare of underlying chronic inflammatory diseases like, ulcerative colitis. Long-term follow-up has confirmed the benign nature of the procedure. Careful informed consent must be obtained and documented. In a recent open label feasibility study published from Massachusetts General Hospital, frozen encapsulated inoculum from unrelated donors (the stool pill) was found to be effective and safe.[11] Formal guidelines need to be in place for best possible outcomes and minimal adverse events.

BRONCHIAL THERMOPLASTY FOR SEVERE ASTHMA

Severe asthma is defined as frequent exacerbations with marked reduction in forced expiratory volume in one second and corticosteroid dependence resulting in poor quality of life.[12] Patients are usually on high doses of multiple medications and experience considerable morbidity from poorly controlled symptoms as well as side effects of medication. The underlying pathologic process that worsens airflow obstruction in chronic asthma is the increase in airway smooth muscle mass and contractility.

A reduction in the muscle mass relieves asthma symptoms. Bronchial thermoplasty (BT) is a novel, procedure based add-on treatment for uncontrolled severe asthma. In BT, a series of bronchoscopic procedures delivers radiofrequency thermal energy to ablate the bronchial wall smooth muscle that reduces its mass and contractility, causing long-term improved asthma control.[13]

The US Food and Drug Administration approved BT in 2010 as the first nonpharmacologic intervention for severe asthma.[12] This was based on an RCT that compared a sham bronchoscopic procedure with BT in symptomatic asthmatics on high dose inhaled corticosteroids and long acting beta agonists.[13] Three procedures were done 3 weeks apart in cases and controls: cases got bronchoscopic thermal ablation and controls got a bronchoscopy without ablation. The findings suggested that BT was effective and safe in reducing exacerbations, hospitalizations and improving quality of life over at least 1 year after the procedure as well as reduction in absenteeism from work. Prior to this there were two other RCTs done that showed its effectiveness. In a recent Cochrane systematic review BT was described to have a modest clinical benefit in quality of life and exacerbation rates in severe asthma without improvement in asthma control scores.[14] In a follow-up study after the sham versus BT clinical trial, it was concluded that reduction in severe exacerbations were maintained for 2 years after BT.[15]

As far as the safety profile is concerned, the risk for complications from bronchoscopy is higher in severe asthma patients including respiratory failure, infections, bleeding and pneumothorax. However, in a well-supervised program the post-treatment safety profile is reasonably acceptable. It should be considered a viable option for intractable asthma symptoms despite optimal pharmacologic therapy but only in medical centers with specialists expertly trained in this procedure. Larger clinical trials are needed to prove a mortality benefit and efficacy for more than 2 years.

MEDICAL MARIJUANA: A POTENTIALLY POWERFUL MEDICATION

Marijuana, a mixture of the dried leaves and flowers from the plant *cannabis sativa*, is the most common illegal recreational drug in the world. It can be smoked to give a high or eaten in baked goods, brewed as tea, or administered in a tablet or liquid form. Globally, 3.5% of the population has used marijuana at least once. It has conventionally been labeled as a drug of addiction with no known medicinal value. However, in the last two decades, attention has shifted to the medicinal properties of marijuana. The premise of labeling it as an addictive drug is based on *insufficient* evidence about its pharmacological properties. Addiction to marijuana is less than 10% and not life-threatening as opposed to alcohol, cocaine or heroin.

Of all the different cannabis compounds, tetrahydrocannabinol (THC) is the psychoactive ingredient that causes altered mood, impairment in movement, thinking, and problem solving as well as hallucinations and paranoia. ***Cannabidiol (CBD) is believed to have medicinal properties without psychoactive effects. It is neuroprotective and has anxiolytic, anticonvulsant, anti-inflammatory, and sedative effects***. It has been suggested that the form of cannabis with a higher proportion of CBD and low amounts of THC can be prepared for use in several debilitating conditions for which traditional medications prove ineffective, though many find it challenging to promote a drug traditionally used recreationally. Current

literature is inadequate and scientifically weak but case reports and case series have been described that are compelling. Research has been difficult due to regulatory limitations. We describe a few conditions that may respond to medical marijuana when traditional treatments have been ineffective.

Multiple Sclerosis

There is definite evidence that marijuana reduces spasticity in multiple sclerosis (MS) and spasm related pain due to its anti-inflammatory properties as shown in 12 trials with 1600 patients.[16] Urinary bladder symptoms, depression, constipation, insomnia, fecal incontinence and defecation urgency have also been relieved. The American National MS Society supports patients who are interested in exploring this option. Marijuana does not reduce tremors, neuropathic pain, or disease progression and may elevate the risk for cognitive impairment. An oral spray *Sativex* is available for prescription use.

Chronic Pain Syndromes

This is the most common use of medical marijuana and it can be used with negligible side effects or addiction in labor pain, migraines, arthritis, cancer pain, pain from spasticity, endometriosis, fibromyalgia, etc. as proven in 6 trials with 325 patients.[16] After robust research of existing literature, the Institute of Medicine (IOM), a highly esteemed peer institution in USA, has deemed that marijuana in any form can cause mild to moderate pain relief on par with codeine.

Cachexia/Wasting Syndrome

Several small clinical trials have demonstrated that marijuana in inhaled or oral form stimulates appetite, stops weight loss, causes weight gain, and reduces nausea more than a placebo in patients with acquired immunodeficiency syndrome (AIDS), cancer or advanced dementia.[17] These effects were found to be long-term. It is well tolerated usually and has low side effects.

Severe Nausea and Vomiting

Dronabinol and Nabilone are synthetic cannabis used for intractable chemotherapy related nausea and vomiting but not as a first line treatment.[17] There are excerpts of doctors allowing patients to smoke marijuana to control nausea.

Amyotrophic Lateral Sclerosis

Cannabis can relieve muscle spasm and pain, improve breathing by relaxing bronchial muscles, reduce drooling by inhibiting saliva, stimulate appetite and sleep, and reduce depression.[18] It does not help in speech, swallowing and sexual dysfunction. Cannabis may slow down the progression of amyotrophic lateral sclerosis (ALS) but can aggravate the already compromised respiratory system and cause death by respiratory failure. It is legally available for use in ALS in 6 States in USA.

Crohn's Disease

Due to its anti-inflammatory properties, patients with Crohn's disease (CD) report a reduction in abdominal pain and cramping, diarrhea, and joint pain with marijuana as proven by a clinical trial.[19] It has minimal side effects and is steroid sparing. Effects are short-term.

Seizure Disorder

Twenty percent patients with epilepsy in USA smoke marijuana and report reduction in seizures, especially in intractable seizure syndromes like, Dravet syndrome, propelling an increase in demand.[20] Large clinical trials are needed to conclusively prove its anti-convulsant efficacy.

Glaucoma

Smoking marijuana reduces pressure within the eyes of all individuals with our without glaucoma but it is short acting and no clinical trials have been done. Side effects include sedation, dry mouth, dizziness, depression, confusion, and weight gain. Eye drops have low penetration.

Post-traumatic Stress Disorder

Many patients with post-traumatic stress disorder (PTSD) smoke marijuana to improve their sleep, appetite and depression and a single study showed reduction in nightmares. Research suggests that it may block negative memories by *reconsolidation blockage*.

Movement Disorders and Dementia

Marijuana may ameliorate a few symptoms in Parkinson's disease, Huntington's disease, and Alzheimer's disease. No large clinical trials have been reported though several are currently ongoing with Sativex spray.

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