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Medical Cannabis and Unanswered Questions in Gastroenterology

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Section I

Since the widespread liberalization of marijuana laws for both medical and recreational uses of cannabis that began in the US in 2014, much attention has been given to possible medical applications in gastrointestinal diseases. I will provide a brief review of the current state of published data and provide suggestions for future research.

There are data that the endocannabinoid system may play a role in the regulation of hepatic inflammation, fibrosis, immune modulation, cellular regeneration and hemodynamic alterations in advanced liver disease [1,2]. However, clinical studies in patients with advanced liver disease are limited. Most human research has been observational and the reported findings are often conflicting. In one study, the fibrosis progressive rate (FPR) in chronic hepatitis C patients was significantly more rapid in daily marijuana users, as compared to infrequent or non-users. Rapid FPR, HCV genotype 3, BMI>30 marijuana use was also associated with increased steatosis [2,3].

Conversely, during liver injury the endocannabinoid system is activated and there is up-regulation of CB1 and CB2 receptors in the liver, particularly in stellate and immune processing cells. CB1 receptors have been proposed to be pro-fibrogenic and CB2 as anti-fibrogenic. Selective activation of CB2 receptors have been shown to reduce fibrosis and promote liver regeneration in rats [4]. There is, also, reason to consider the possibility that CB1receptor antagonism might be a factor in preventing NASH and that is a fertile area for research interest [5].

Despite multiple postulated mechanisms of action for salutary effects of cannabis intreating liver disease and scattered anecdotal testimonials of effectiveness, there are no evidence-based data that cannabis has an anti-viral effect on hepatitis C (now, perhaps, a moot point because of the proliferation of highly effective DAA agents).

Section II

There is interest in the use of cannabis in treating Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis) where published data reflect widespread cannabis self-medication by patients [6-11]. In these reports a substantial portion of patients perceived cannabis as effective for relief of abdominal pain, anorexia and nausea. Nearly half of non-users expressed interest in cannabis use if it were legal [7].

Numerous mouse studies have provided data that cannabinoids could have a protective effect in the sodium dextran sulfate colitis model via central and peripheral mechanisms [8]. Other published animal data with different potential mechanisms of action exist as well [9-12]. Clinical data in humans are largely self-reported and observational and suggest improved symptom management and steroid sparing but have not demonstrated mucosal healing [13,14].

Section III

There is considerable evidence in animal models and human data that manipulation of the endocannabinoid system can reduce nausea and vomiting. Activation of CB1 receptors suppresses vomiting which is reversed by CB1 antagonism. Among emetic species of laboratory animals, cannabidiol suppresses nausea and vomiting within a limited dose range [15]. Multiple possible mechanisms of action have been proposed [16,17]. Clinical data suggest that cannabinoids have similar effects as FDA approved agents for nausea and vomiting and FDA approved synthetic THC products are available for this indication [18,19].

There is, however, concern that cannabis products are, paradoxically, implicated in an irrefutable increase in the marijuana hyperemesis syndrome which is usually characterized by at least weekly use of MJ for more than one year [20-26].

Conclusion

In conclusion, there is increased interest among both the lay and professional population about the safety and effectiveness of medical cannabis. Although there are many reasons to believe safe and effective disease specific applications are likely to exist, there is a paucity of evidence-based data and randomized clinical trials to justify their general adoption in medical practice. A more complete understanding of the most appropriate delivery systems, specific cannabinoid derivatives and ratios with their respective pharmacodynamics and pharmacokinetics, dosing and the relative

roles of plant-derived and synthetic products will be necessary before fully safe and effective pharmaceutical agents will be generally available.

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