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IBD patients find symptom relief in the Cannabis field

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Abstract

Cannabis (or marijuana) has been used in traditional medicine to treat intestinal inflammation and is used as a self-medication by patients with inflammatory bowel disease (IBD). A survey by Ravikoff Allegretti et al.¹ at a specialized IBD clinic shows that, in the US, marijuana is used by a significant number of patients with IBD to alleviate their symptoms.

In gastroenterology, Cannabis is known for its antiemetic, appetite stimulating and antidiarrheal effects. Despite the well-characterized impact of cannabinoids in experimental intestinal inflammation,² knowledge on the potential benefits of cannabinoids in human IBD is largely based on anecdotal reports. There is strong evidence from basic science that cannabinoids protect against and alleviate intestinal inflammation in mice, but for human IBD, cannabinoid effects remain to be established yet in clinical trials. Ravikoff Allegretti et al. have presented a prospective survey study on 292 IBD patients revealing that a significant number of IBD patients in the US (16.4 %) have used Cannabis to treat symptoms, such as abdominal pain, loss of appetite, nausea and diarrhea.¹ The majority of the patients reported that Cannabis was “very helpful” in reducing these symptoms. A further important aspect of their study was that not only patients with Crohn’s disease but also patients with ulcerative colitis classified Cannabis as “very helpful”. Using multivariate analysis, the authors further identified that age and abdominal pain were the strongest predictors for the use of Cannabis in IBD patients. Without doubt, the present survey supports the traditional view that Cannabis provides benefit in disturbances of the gastrointestinal tract, especially in abdominal pain.

Their results confirm a 2011 published survey in a Canadian population by Lal et al. in which chronic abdominal pain and a history of abdominal surgery were reported as primary reasons for the use of Cannabis.³ One prospective uncontrolled observational study already found improved quality of life and reductions of disease activity in patients with IBD who were advised to smoke cigarettes with Cannabis, whenever they felt pain.⁴ Thirteen patients were included and were provided with 50 g dry Cannabis per month for the on demand treatment. All patients used the full amount and additional use of Cannabis was not captured. A recently published prospective placebo controlled clinical trial by Naftali et al. where patients with Crohn’s disease received two cigarettes with 11.5 mg tetrahydrocannabinol (THC) per day for 8 weeks found significant clinical benefits in the THC-treated patients in the secondary analyses but the primary end point of induction of remission was not achieved.⁵ Interestingly, no relevant side effects were reported.^{4,5} From both studies we learn that there may be a role for Cannabis in the treatment of IBD but further information may help to select the right group of patients for which Cannabis may be

beneficial. Cannabis may help in Crohn's disease, ulcerative colitis or in both, in induction or maintenance of remission of these diseases. Thus, epidemiological data are needed to direct future clinical trials.

What are the mechanisms behind these beneficial effects? The discovery of THC as the psychoactive agent of Cannabis and the discovery of the endocannabinoid system paved the road to the understanding of how Cannabis affects our organism. This system may be regarded as an endogenous molecular network involved in pain and inflammation like the endovanilloid system or the endogenous opioid system.² THC and other cannabinoids bind to cannabinoid receptors (Cannabinoid receptor 1 and 2; CB₁ and CB₂) which are expressed in the central and peripheral nervous systems (CB₁ and CB₂), in leukocytes (CB₂) and elsewhere.⁶ The picture of the endocannabinoid system was completed when the endogenous ligands of the cannabinoid receptors (endocannabinoids), i. e. anandamide (AEA) and 2-arachidonoylglycerol (2-AG), were detected. Fig. 1 depicts a basic introduction into the structure of the endocannabinoid system which consists of the canonical cannabinoid receptors (CB₁, CB₂), their endogeneous ligands AEA and 2-AG and their synthesizing and degrading enzymes. Use of Cannabis during IBD most likely influences inflammation and pain via cannabinoid and possibly other receptors⁷ thereby influencing downstream regulation within the endocannabinoid system.

However, the survey by Ravikoff Allegretti et al. indicates that Cannabis is particularly helpful in alleviating abdominal pain and nausea while relief of diarrhea was reported less often.¹ Also in the Canadian survey, Lal et al. noticed that the number of patients reporting relief of abdominal pain was higher than the one reporting relief of diarrhea.³ The survey studies highly suggest that IBD patients with pain may be the best target for Cannabis-based treatments. Thus clinical studies in IBD patients investigating effects of Cannabis on pain and on maintenance of remission are wanted, whereas Cannabis may not be correctly placed in the induction of remission.

The endocannabinoid system is integral part of the colon and in patients with active IBD, specific changes support a local regulatory role in intestinal inflammation.^{8,9} AEA and its synthesizing enzyme (NAPE-PLD; see Fig. 1) display lower levels in ulcerative colitis while expression of CB₂ and enzymes responsible for synthesis and degradation of 2-AG (DAGL and MAGL, resp.; see Fig. 1) are increased.^{8,9} The CB₂ receptor and 2-AG in the colon therefore may represent crucial players in the healing process of human IBD. However, we have learned that targeting the endocannabinoid system at specific sites, e.g. at the CB₁ or the CB₂ receptor, may have different maybe even opposing effects, and future clinical trials should therefore use more specific compounds rather than THC (which acts as a CB₁ and a CB₂ receptor agonist) in order to specifically characterize influences of the different targets on patients symptoms. Additionally, from a medical perspective we should come up with more intelligent routes of application for Cannabis since smoking may not only induce lung cancer and other serious illnesses. In the context of Crohn's disease, smoking is a well established independent risk factor.¹⁰

In summary, the survey by Ravikoff Allegretti et al. strongly suggests that in patients with IBD, self-medication with Cannabis may improve abdominal pain and nausea and may be a promising option for alternative IBD treatment.¹ However, all aforementioned studies have limitations by being uncontrolled or too small. As the authors point out, clinical trials are warranted to determine efficacy, safety and side effects of a Cannabis-based treatment and this survey study will help to identify the ideal patient selection. With the legalization of medical marijuana in several states of the US and the observation that almost half of non-Cannabis users in the present survey would be interested to participate in a trial, Cannabis has become a realistic and feasible therapeutic possibility for IBD. Presently though,

Cannabis can not be recommended for the treatment of symptoms associated with IBD but from a medical perspective, clinical trials exploring such opportunities are wanted.

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Fig. 1. Scheme of the endocannabinoid system

The endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are synthesized and released on demand in a paracrine fashion. N-arachidonoylphosphatidylethanolamine (NAPE) needs arachidonic acid as a precursor and is cleaved by a phospholipase D (NAPE-PLD) into AEA. The key enzyme in synthesizing 2-AG from diacylglycerol (DAG) is diacylglycerol lipase (DAGL). AEA and 2-AG primarily activate cannabinoid receptors (cannabinoid receptor 1 and 2; CB₁, CB₂) but AEA may also act as a ligand for the transient receptor potential cation channel 1 (vanilloid receptor 1; TRPV1) and the G protein-coupled receptor 55 (GPR55). The existence of an endocannabinoid transporter (EMT) is still controversial. The main enzyme in degrading AEA is fatty acid amide hydrolase (FAAH) while 2-AG is degraded by monoacylglycerol lipase (MAGL). The EMT, the GPR55 and the TRPV1 receptor may not be part of the endocannabinoid system in a close sense but were added to the system as they are responsive to and involved in the action of exo- and endocannabinoids.