Twelve years ago Leo Hollister (1986) published a review on health aspects of cannabis which can truly be called a ‘classic’. In a field where emotions, prejudices and personal preferences frequently supplant objectivity, Hollister drew a picture not only solidly based on clinical studies – some of which came from his laboratory – but also on his thorough knowledge of drug dependence and medicine and on his common sense. For over a decade, at meetings, ‘Hollister says’ meant his 1986 review. He has now revisited the field, again demonstrating his mastery of the topic. In the 1986 review a portion was devoted to therapeutic uses. This aspect has not been revisited now, which we can only regret. I certainly would have liked to hear what he has to say on the debate on ‘medical marijuana’, on the clinical advantages of marijuana versus THC (or vice versa), and on specific issues such as the use of marijuana in multiple sclerosis, which is widely used by patients. Such a use is not supported in the US by the National Multiple Sclerosis Society, while in the UK, the British Medical Association strongly recommends ‘carefully controlled trials of cannabinoids in patients with chronic spastic disorders which have not responded to other drugs’. Such trials merit a high priority (British Medical Association, 1997).

Has the overall attitude to therapeutic uses of cannabis and cannabinoids changed over the last decade? In my view, the answer is positive. Δ⁸-Tetrahydrocannabinol (Δ⁸-THC) (marinol, dronabinol) is now an approved drug for appetite stimulation and against emesis in the US. In Germany it was recently approved as an ethical drug for unspecified use. The market in the US is not very large due to the side effects associated with THC use, and its relatively high price. Marijuana, although illegal, is apparently less expensive, acts faster and is claimed to be less anxiogenic. The latter claim may have a biochemical basis – marijuana contains relatively high levels of the psychotropically inactive cannabidiol which has been shown to reduce anxiety in animals and (in one publication) in human subjects (Zuardi et al., 1982).

A strong lobby for the decriminalization of ‘medical marijuana’ has succeeded in having its use approved by referendum in two states – Arizona and California. This approval will lead in the near future to a relatively large number of users who have smoked marijuana for a variety of real, imaginary or self-proclaimed disorders. This situation will compel the regulatory authorities to obtain reliable data on safety and efficacy. Cannabis, like all other plants, hosts a variety of microorganisms, some of which represent a health hazard. It seems plausible therefore that commercial ‘medical marijuana’, although illegal or almost illegal, will have to comply with certain quality regulations established by health agencies which possibly oppose cannabis use. An unique situation!

In the 1986 review Hollister looked at the therapeutic data available. Some, but not many, indications have changed.

**Antiemetic action**

Surprisingly, in spite of the enormous public interest in ‘medical marijuana’ and countless articles in the daily press and magazines focused predominantly on this aspect of marijuana use, little progress has been reported on the antiemetic activity of cannabinoids in the last decade. Plasse et al. (1991) have reviewed the clinical experience gained over several years with dronabinol (Δ⁸-THC) in antiemetic treatment. With doses of 7 mg/m² or below, complete response was noted in 36% of the patients, 32% showed partial response and 32% showed no response. However, 65% displayed drowsiness and dizziness and 12% had dysphoric effects. Combination treatment of dronabinol with prochlorperazine was more effective than each drug alone. This is not an outstanding record. The HT₃ blockers now available are much more effective. It is of interest that Δ⁴-THC can be administered at higher doses to young children than to adults without causing psychotropic side effects, with complete block of nausea and vomiting (Abrahamov et al., 1995). These results are from a single, open trial. If confirmed, we may have an additional drug, whose effects in children differ from those in adults.

Comment on ‘Health aspects of cannabis: revisited’ (Hollister)

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Appetite stimulation

THC appears to be ineffective in anorexia nervosa. In retrospect, this is not surprising as this disease is characterized not by lack of appetite, but by a strong compulsion to refuse food.

Dronabinol is now an FDA-approved drug for the treatment of cachexia and is prescribed to cancer and AIDS patients. The clinical literature however is limited. Plasse et al. (1991) reported the results of two multicentre, open studies on the effects of dronabinol as an appetite stimulant in cancer patients. Various doses and dose schedules were followed and side-effects versus dose levels were evaluated. Their conclusion was that ‘overall, no group gained a significant amount of weight while on the study, though some individual patients did actually gain weight. However, there was a reduction in the rate of weight loss in all groups’. The reduction in the rate of weight loss was significant for the groups administered 2.5 and 5 mg four times a day. Psychotropic effects were not noted at the lower dose; weakness and fatigue, dizziness, drowsiness and memory or concentration difficulties were recorded at the higher dose.

In a later study (Beal et al., 1995), the effects of dronabinol (2.5 mg, twice a day) on appetite, weight, nausea and mood were examined in 139 AIDS patients over a 6-wk period. After 4 wk, significant differences in anorexia were seen and these were sustained throughout the trial. Weight was stable in the treated patients, but was lower in the placebo recipients. The data indicated that dronabinol caused increased appetite (38%), decreased nausea (20%) and some improvement in mood. The side-effects noted were minor and were not severe enough to require intervention. A small number of patients, who received only 2.5 mg once a day due to the side-effects, showed an appetite increase similar to that of patients treated with dronabinol twice a day. This low dose of THC is not expected to produce any significant side-effects. The authors of this study conclude that ‘dronabinol is a safe and effective treatment for anorexia in patients with weight loss due to AIDS. By improving appetite and mood, decreasing nausea, and stabilizing weight, dronabinol may significantly improve the quality of life of patients infected with HIV’.

Cannabinoids have immunosuppressive effects. As AIDS patients are immunocompromised already, do cannabinoids add insult to injury? The limited research on this topic has failed to find such an effect, but more detailed investigations are certainly needed.

Multiple sclerosis (MS)

Several anecdotal reports have appeared which indicate that cannabis can alleviate symptoms of MS. The clinical trials reported so far are rather limited. A typical one is by Petro and Ellenberger (1981), who reported that in a group of 9 patients administered up to 10 mg THC, three felt that they were better able to walk. The authors measured deep tendon reflexes, muscular resistance to stretch of the legs and abnormal reflexes and found improvements. Studies in rats with an experimental model (experimental autoimmune encephalomyelitis) support the preliminary clinical studies (Wirguin et al., 1994). However in contrast, other clinical reports found either no improvement in MS patients who smoked marijuana on a single occasion, or noted objective improvements in only a few patients.

Consroe et al. (1997) have analysed the answers to a questionnaire mailed to MS patients who use cannabis regularly. The 112 patients who responded to the questionnaire were about equally divided between USA and UK and between male and female patients. Most of the patients (between 87 and 96%) reported strong improvement after cannabis in spasticity at sleep onset, and on awakening at night, as well as reduction of leg pain at night and tremor. The patients also reported improvement in anxiety and depression as well as in spasticity when awakening in the morning and on walking. There was only minor improvement in memory loss, faecal incontinence and in constipation.

The overall situation as regards other disorders, such as glaucoma, asthma, epilepsy, hypertension, etc. does not differ from that of MS: there are positive preclinical studies for most of these disorders: anecdotal reports or preliminary clinical studies have been published, but a definitive answer is impossible at present. Are we missing something?

References


