Summary

The current research project was conducted as part of the research programme "Research Programme in support of the federal drugs policy document " This project aims at explaining the present knowledge regarding the effectiveness and efficiency of the medicinal use of cannabis and cannabinoids by means of meta-analysis. Because of the variety of the possible medical applications of cannabinoids in clinical practice, it is impossible to formulate general conclusions regarding the therapeutic value of cannabis. Therefore we have analysed the results of scientific reports on the effects of different cannabinoids for different indications.

In the first stage of this inquiry we conducted a profound analysis of the literature, which resulted in a database of 169 clinical trials, pilot studies, surveys and case studies. These sientific publications were then classified according to symptomatology. In consultation with the members of the steering committee of this research project we decided to conduct meta-analyses on the medicinal use of cannabis in cancer- and AIDS-related anorexia and cachexia, Tourette's Syndrome (TS) and multiple sclerosis (MS)-related spasticity. The decision for conducting these meta-analyses was based on the fact that at present no meta-analytic research on these topics has been reported as well as the fact that the results of our literature analysis show that the vast majority of scientific literature on the medicinal use of cannabis covers these topics. In addition, we analysed and evaluated a recently published meta-analysis on the anti-emetic efficiency of cannabinoids in chemotherapy as well as a recent qualitative study on the analgesic properties of cannabinoids. We also updated the findings of these studies with the results of more current research.

In the second stage of our research we analysed the methodological quality of all the scientific publications on the selected research topics by means of the Oxford Scale (Jadad, Moore, Carroll et al., 1996). This scale consists of 3 items to score the degree of randomization, blinding and the description of dropouts / withdrawals in clinical trials. Given the social and political impact of the current research project, we applied strict criteria for the evaluation of experimental methodology and scientific quality. Research that did not meet these requirements was excluded from the meta-analysis.

Our analysis of scientific literature concerning the therapeutic application of cannabinoids in cancer- and AIDS-related anorexia and cachexia shows that for these symptoms a meta-analysis is not feasible due to the lack of conformity in the translation of abstract concepts into operational terms and presentation of the results. The relevant question regarding this topic is, however, whether in contemporary Western medicine there is a need for cannabis based medication to improve one's appetite. Recent research findings illustrate the effectiveness and safety of megestrol acetate as an appetite stimulant in cancer- and AIDS-related anorexia and cachexia (Pascual Lopez, Roque I Figuls, Urrutia Cuchi et al., 2004).

It neither is possible to conduct a meta-analysis on the medicinal use of cannabinoids in anorexia and cachexia related to Alzheimer's disease (AD), because only a single clinical trial has been reported on this topic. Current research now rather focusses on the reduction of agitation in AD. Indirectly this has implications for the symptom treatment of anorexia, given the fact that recent research findings suggest that behavioural problems related to AD are a causal factor in the development of anorexia (White, McConnell, Bales et al., 2004). It is, however, still too early to draw scientific conclusions regarding the effectiveness and efficiency of the medicinal use of cannabis and cannabinoids in anorexia and cachexia. Not only is there a need for multicentre scientific research, the therapeutic application of cannabinoids in AD can also lead to a profound ethical debate.

The most large scale and qualitatively outstanding study that has been performed on the medicinal use of cannabis, was charged by the House of Lords in Great-Britain. They had looked at the issue of medicinal use of cannabis and recommended further studies. This resulted in a a large (660 patient) multicentre, randomised, double blind, controlled trial on the therapeutic value of cannabinoids in MS-related spasticity (see Zajicek, Fox, Sanders et al., 2003). Results show that treatment with cannabinoids did not improve spasticity when measured objectively, but the effect of spasticity and pain as assessed by patients indicates a symptomatic subjective clinical effect. A possible explanation for this discrepancy in results is that the objective measures that were used are too insensitive to identify small but clinically significant effects on spasticity (Zajicek, Fox, Sanders et al., 2003).

Our analysis of the research regarding the therapeutic application of cannabis in TS shows that all the scientific publications on this topic have been reported by the same group of researchers, i.e. the group of Müller-Vahl in the Medizinische Hochschule Hannover,

Germany. The 5 existing publications that were analysed resulted from just 2 clinical trials. In these trials there is an overlap of the patients: some participated in both studies. Moreover, due to the lack of conformity in the presentation of the results and the unavailability of individual patient data, it was impossible for us to perform a qualitative analysis. In accordance with the research findings of Zajicek, Fox, Sanders et al. (2003), Müller-Vahl et al. found that treatment with cannabinoids significantly improved TS-symptoms when assessed by patients, but hardly found a significant treatment effect when objective measures were applied (Müller-Vahl, Schneider, Koblenz et al., 2002 ; Müller-Vahl, Schneider, Prevedel et al., 2003). These findings may also be explained by the difference in sensitivity of the measures that were used.

Up until now medicinal cannabis has been studied most frequently in the context of chemotherapy-related emesis. The vast majority of scientific literature dates from the first half of the eighties. Also, it is the only indication for which a meta-analysis on the therapeutic application of cannabinoids has been published. This meta-analysis shows that cannabinoids are effective anti-emetics, but that treatment with cannabinoids can result in potentially harmful side effects compared to the side effects that may be caused by other anti-emetics (Tramèr, Carroll, Campbell et al., 2001). During the past decade hardly any scientific research on the anti-emetic value of cannabis has been published. Scientific reports on the positive results that are obtained with more recently developed anti-emetics, such as serotonin-receptor-agonists, are now published regularly. This progress in the treatment of chemotherapy-related emesis as well as the fact that treatment with cannabinoids can cause potentially harmful side effects, has lead to the fact that there is no longer a demand for cannabinoids as anti-emetics.

Currently, the major topic of interest regarding the medicinal use of cannabis is the research on its analgesic value. In 2000 Campbell, Tramèr, Carroll et al. (2001) assessed the feasibility of meta-analytic research on this topic. Because of the methodological differences of the different reports it was not possible to conduct a quantitative analysis. A qualitative analysis of these publications shows that cannabinoids are no more effective than codeine in controlling acute pain and show a dose-response relation for adverse psychotropic effects (Campbell, Tramèr, Carroll et al., 2001).

At present research primarily focusses on the analgesic value of cannabinoids in neuropathic pain. Since 2003 5 randomised, double blind, placebo-controlled clinical trials on this topic have been published in international peer-reviewed journals. All these publications report a significant reduction in pain as a result of treatment with cannabinoids. Our analysis of very recent scientific literature suggests that in the near future (i.e. at the end of 2005) it will be possible to conduct a meta-analysis based on the results mentioned in these reports as well as the results of ongoing research, which will be published in the next few months.

With regard to future research we would like to make the following recommendations. The current research project aimed at explaining the present knowledge regarding the effectiveness and efficiency of the medicinal use of cannabis and cannabinoids. Despite the progress in understanding the pharmacology and neurobiology of cannabinoid systems, this field is still in full development (Childers & Breivogel, 1998). This implies that the range of application of cannabinoids might change or expand in the near future. We therefore recommend more large scale clinical trials for these possible new uses of cannabis, similar to the study by Zajicek, Fox, Sanders et al. (2003) on the medicinal use of cannabinoids in MS-related spasticity.

We consider it advisable that future research will focus on the development of diagnostic measures that are able to identify small but clinically significant effects. We also consider it necessary that these measures will be generally applied in cannabis research and that the results obtained by those measures will be reported in a similar manner. That way it will be possible to quantitatively compare results of diffrenent studies in a meta-analysis.

Our research shows we were unable to get access to the individual patient data of the selected studies. We would therefore like to recommend an improvement in the access to individual patient data of different studies. This may for example become possible through the set up of database(s) on the internet. This availability would definitely contribute to meta-analytic research.

In conclusion we would like to point out that for most indications it currently isn't feasible to conduct meta-analyses on the medicinal use of cannabis. This, however, does not imply that treatment with cannabinoids does not lead to improvement of the studied symptoms. It does

imply that for now it is impossible to draw scientific conclusions regarding the effectiveness and efficiency of the medicinal use of cannabis and cannabinoids for these symptoms.

"…the absence of evidence of effect is not the same as evidence of absence of effect…"

(Campbell, Tramèr, Carroll et al., 2001)

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