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Review

Efficacy and safety of medical cannabinoids in older subjects: A systematic review

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ABSTRACT

This systematic review aims to integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects. The literature search was conducted using PubMed, EMBASE, CINAHL and Cochrane Library. We selected controlled trials including solely older subjects (≥65 years) or reporting data on older subgroups. 105 (74%) papers, on controlled intervention trials, reported the inclusion of older subjects. Five studies reported data on older persons separately. These were randomized controlled trials, including in total 267 participants (mean age 47–78 years). Interventions were oral tetrahydrocannabinol (THC) ($n=3$) and oral THC combined with cannabidiol ($n=2$). The studies showed no efficacy on dyskinesia, breathlessness and chemotherapy induced nausea and vomiting. Two studies showed that THC might be useful in treatment of anorexia and behavioral symptoms in dementia. Adverse events were more common during cannabinoid treatment compared to the control treatment, and were most frequently sedation like symptoms. Although trials studying medical cannabinoids included older subjects, there is a lack of evidence of its use specifically in older patients. Adequately powered trials are needed to assess the efficacy and safety of cannabinoids in older subjects, as the potential symptomatic benefit is especially attractive in this age group.

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1. Introduction

For many centuries the cannabis plant (*Cannabis sativa* L.) has been used worldwide for medical as well as recreational purposes. Possible indications of cannabis, such as cancer pain, cachexia and neuropathic pain, are found in a quickly growing population of older patients. Unfortunately, there are only limited data on the extent of the use of medicinal cannabinoids in older persons. Although international web-based surveys show only a low percentage of older users, in the Dutch setting, more than one third of patients using medicinal cannabis on prescription are over 60 years (Hazekamp and Heerdink, 2013; Hazekamp et al., 2013). On the one hand, this group may highly benefit from medical application of cannabis, because of a greater emphasis on symptomatic and palliative effects of medication, which is directly related to their limited life expectancy. On the other hand, an increased vulnerability of the brain, due to a reduction in cognitive functioning and brain atrophy (Savva et al., 2009; Singh-Manoux et al., 2012) and age related changes in pharmacokinetic factors (Mangoni and Jackson, 2004) may result in more severe adverse effects.

Cannabis preparations contain numerous cannabinoids, including delta-9-tetrahydrocannabinol (THC), with psychoactive effects, and cannabidiol (CBD), with neuroprotective, anticonvulsive, antiemetic and anti-inflammatory effects, as the major constituents. These cannabinoids act upon an endogenous cannabinoid system of which two receptors (CB_1 and CB_2) have been identified (Matsuda et al., 1990; Munro et al., 1993). These receptors are mainly located in the central nervous system (CB_1 and CB_2) and the immune system (CB_2) (Herkenham et al., 1990; Onaivi et al., 2006).

Several trials studying the efficacy of medical cannabinoids have been conducted, covering a wide range of diseases and conditions, including neuropathic pain, chemotherapy-induced nausea and vomiting and loss of appetite (Iskedjian et al., 2007; Jatoi et al., 2002; Lever and Rice, 2007; Ware et al., 2008). Unfortunately, data on efficacy and safety established in studies with adults cannot simply be extrapolated to the older patient group, due to changes in pharmacokinetic and pharmacodynamic factors associated with increasing age, leading to differences in efficacy and a high risk of developing adverse drug reaction. This can result in drug-related morbidity, hospital admission and mortality (Mannesse et al., 1997; Routledge et al., 2004). Examples of changes in pharmacokinetic factors associated with increasing age are a decreased lean body mass, reduction of renal and hepatic clearance and loss of ability to maintain homeostasis (Clegg et al., 2013; Lindeman et al., 1985). The high prevalence of co-morbidity and related polypharmacy further complicates drug treatment in this population. It is therefore highly relevant to study the effects of medical cannabinoids in older patients separately, before advocating wide spread use.

To date, no review on the efficacy and safety of cannabinoids in older patients has been conducted. Although, the Cochrane Collaboration published a systematic review on cannabinoids in dementia patients (Krishnan et al., 2009), including one small randomized controlled trial (RCT) studying the efficacy of nabilone on anorexia and behavioral disturbances in subjects with severe dementia (Volicer et al., 1997). In the current systematic review we aimed to provide broader evidence on the safety and efficacy of medical cannabinoids in older subjects, independent of the reasons for prescription or the patients' cognitive status.

2. Methods

2.1. Search strategy

We performed a search of PubMed, EMBASE, CINAHL and Cochrane Library databases up to October 7th 2013 for articles published in English. For PubMed, a comprehensive search was developed, which was adapted to the other databases (see appendices). The search strategy and eligibility criteria were specified in advance and documented in a study protocol. Relevant search term synonyms were determined using Thesaurus and discussion with experts. We used the following terms to determine the subject group: 'aged', 'frail', 'elderly', 'older', 'aging', 'ageing' and 'geriatric'. To determine the intervention we used the terms: 'cannabinoids', 'cannabinoid', 'cannabinol', 'cannabidiol', 'tetrahydrocannabinol', 'marinol', 'cesamet', 'THC', 'CBD', 'sativex', 'nabilone', 'dronabinol', 'delta-9-tetrahydrocannabinol','delta-THC', 'cannabis', 'marihuana', 'marijuana' and 'hasish'. The existing clinical query 'Therapy/Broad' was used in PubMed to select therapeutic studies. Duplicate publications were selected and removed. The final results were ranked alphabetically and received an article specific number.

2.2. Eligibility criteria

Two reviewers (GE and ML) conducted the search by independently examining the title and available abstract of each article, in an unblinded manner. Studies were considered for inclusion when they: (1) included exclusively older subjects (defined as ≥65 years) or a distinct subgroup of older subjects and provided separate results on this subgroup; (2) studied the efficacy, safety or pharmacokinetics of medical cannabinoids administered by any route, at any dose and for any duration; (3) were prospective, controlled intervention trials and; (4) provided data on efficacy, safety, or pharmacokinetics. Studies were excluded when they (1) included exclusively younger subjects (<65 years); (2) studied cannabinoids for recreational purposes; (3) studied endocannabinoids or cannabinoid antagonists. Articles that seemed to meet the eligibility criteria based on title or abstract were screened in full-text by the same reviewers (GE and ML). In case of disagreement or uncertainty two other researchers (MM and MOR) were consulted to reach consensus. The snowball method was used to manually identify relevant references from the reference lists of included articles.

2.3. Data extraction and assessment of methodological quality

A modified Cochrane data extraction sheet was used to extract data from the included articles. Data collection included study design, participant characteristics (including age, gender and number of participants), intervention indication, intervention, outcome measures, results, data on adverse events and pharmacokinetics. The corresponding authors of the included studies were contacted to request details on subject characteristics, study conduct, primary