MDH Minnesota Department *of* Health
OFFICE OF MEDICAL CANNABIS

Schizophrenia

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Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies of cannabis therapy are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Though the MN medical cannabis program does not allow smoked or vaporized dried cannabis, studies using these forms of cannabis administration were allowed for insight they could provide. Finally, the federal government-maintained web site of clinical trials, clinicatrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

Schizophrenia has been identified as a major psychotic disorder for over a century and how it has been conceptualized has evolved over time. It is now understood to have six core domains (Nasrallah 2011):

1. Positive symptoms – including the psychotic symptoms of delusions and hallucinations

2. Disorganization of speech and behavior
3. Negative symptoms – including amotivation and blunt or flat affect
4. Cognitive deficits – including severe impairments in memory, executive functions, and learning
5. Mood symptoms – including depression and suicidal urges as well as hostility and aggression
6. Neuromotor symptoms – including varying degrees of catatonia, stereotypic movements, and dystonia

In its typical course, a prodromal phase with attenuated positive symptoms and declining function appears in late adolescence or early adulthood. Within relatively few years a first psychotic episode heralds the formal onset of schizophrenia. The next decade is generally marked by repeated episodes of psychosis with partial and variable degrees and duration of inter-episode remission with accrual of disability with each episode of illness. Finally, a stable phase or plateau develops, when psychotic symptoms are less prominent and negative symptoms and the stable cognitive deficits increasingly dominate. Recovery of varying amounts can occur at any stage of the illness and, though most patients experience progressive deterioration over time, some show substantial improvement (Tandon 2009).

Schizophrenia is one of the most disabling of psychiatric disorders with profound effects on affected individuals and their families. It is associated with increased likelihood of unemployment and homelessness, with less than one-fifth of affected individuals fully employed (Tandon 2009). Families of patients with schizophrenia, in comparison with families of patients with other chronic diseases, report higher burden and lower support from their social networks and from professionals (Magliano 2005).

Prevalence

A systematic review of epidemiological studies from multiple countries estimates 7 persons per 1000 will develop schizophrenia during their lifetime. Prevalence is higher among immigrants, in more highly-developed countries, and at high latitude (McGrath 2008). Schizophrenia runs in families and it is estimated that genetic factors contribute around 80% of risk for developing the disease (Nasrallah 2011).

Current Therapies

The mainstay of current therapy is a wide variety of antipsychotic drugs. These drugs have been shown to have some efficacy at reducing positive symptoms (hallucinations and delusions) and reducing relapse, but produce only limited improvement in negative symptoms, cognitive function, social functioning, and quality of life. Their side effects are often quite troubling, notably neurological movement disorders in the medications introduced in the 1960s and 1970s (examples: chlorpromazine, haloperidol) and metabolic disorders in medications introduced subsequently. Drugs from a variety of classes (anticonvulsants, antidepressants, benzodiazepines, lithium) are used as adjuncts to antipsychotic medications in targeting specific

symptom domains – usually with modest benefits. About a third of patients with schizophrenia continue to suffer from persistent psychotic symptoms despite adequate pharmacotherapy. The limited efficacy of the drugs is exacerbated by the common occurrence of patients not taking their prescribed medications. A comprehensive, multi-modal approach to treatment is recommended, including medication, psychosocial interventions, and assistance with housing and financial sustenance. A variety of psychotherapies and social treatments are used – when tested, they generally show only limited benefit. Finally, there is great variability in how an individual person responds to a particular medication or psychotherapy, so there is an element of trial and error in identifying the best treatments for a specific patient (Tandon 2010).

Though there have been many developments in the treatment of schizophrenia over the past few decades, there remains great need for better therapies. As one recent review summarizes the situation, "The current standard treatments, both pharmacological and psychosocial, remain limited and inadequate as evidenced by partial response and functional disability in the majority of patients at this time … There is a tremendous need in the pharmacotherapy of schizophrenia including a safer and more effective treatment for positive symptoms, a treatment for negative symptoms, and a treatment for cognitive deficits" (Nasrallah 2011). There is a large volume of research now under way to identify agents and molecular targets to effectively treat the various symptom domains of schizophrenia (Tandon 2010).

Pre-Clinical Research

Research results published to date make a compelling case for involvement of the endocannabinoid system in schizophrenia, but the nature of that involvement is still quite unclear. Much of the interpretation of pre-clinical study findings remains speculative. The review articles found for this briefing combined discussion of pre-clinical, clinical, and epidemiologic studies and sometimes they include discussion of cannabinoids as both promoters of and therapy for schizophrenia; they are included in the OBSERVATIONAL STUDIES section of this document.

Clinical Trials

One published clinical trial of a cannabis constituent (CBD) as therapy for schizophrenia was found (Leweke 2012). Three additional clinical trials present on The Clinical Trials Website www.clinicaltrials.com (one completed and two now recruiting patients) are identified and summarized below.

Leweke FM, Peimelli D, Pahlisch F, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry* 2012; 2:e94 (7 pages).

42 patients with acutely exacerbated schizophrenia were randomized to a double-blinded four week trial of oral cannabidiol or the potent antipsychotic drug, amisulpride (dopamine receptor blocker). Enrolled patients were hospitalized for at least the four weeks of the study. Patients

in both groups had significant clinical improvement, with no difference between groups. CBD displayed a much better side effect profile. CBD treatment was accompanied by a significant increase in serum anandamide levels, which was significantly associated with clinical improvement. "These results suggest that inhibition of anandamide deactivation may contribute to the antipsychotic effects of cannabidiol potentially representing a completely new mechanism in the treatment of schizophrenia."

"A Study of GWP42003 as Adjunctive Therapy in the First Line Treatment of Schizophrenia or Related Psychotic Disorder" NCT02006628
https://clinicaltrials.gov/ct2/show/NCT02006628?term=cannabis+schizophrenia&rank=21

This clinical trial is reported as completed in 2015 on The Clinical Trials Website www.clinicaltrials.gov. No results are posted on The Clinical Trials Website www.clinicaltrials.gov, and results have not been published, but the research sponsor, GWPharma, has announced top-line results. The trial enrolled 88 adults with schizophrenia in the UK, Poland, and Romania. Patients were randomized to 500 mg CBD in oral solution twice daily or placebo in addition to their existing, stable dose of anti-psychotic medication for six weeks of treatment. Primary outcome measures included Positive and Negative Syndrome Scale (PANSS) total score and Positive, Negative, and General subscales, Scale for the Assessment of Negative Symptoms (SANS) score, Clinical Global Impressions – Severity Scale (CGI-S), Clinical Global Impressions – Improvement Scale (CGI-I), and Carer and Participant Global Impression of Change scales (CGIC and PGIC). In September, 2015 GW Pharmaceuticals announced that in the trial cannabidiol showed consistently greater improvement over placebo with respect to PANSS-positive subscale (p=0.018), CGI-S (p=0.04), and CGI-I (p=0.02).

"A Four-week Clinical Trial Investigating Efficacy and Safety of Cannabidiol as a Treatment for Acutely Ill Schizophrenic Patients" NCT02088060
https://clinicaltrials.gov/ct2/show/NCT02088060?term=cannabis+schizophrenia&rank=25

This clinical trial is now recruiting patients and has an estimated completion date of December, 2016. An anticipated 150 adults with schizophrenia diagnosis ≤3 years will be recruited in Denmark and Germany. Patients will be randomized to one of three arms for the four week trial: 1)CBD 300 mg tablets twice/day and placebo olanzapine capsule once/day; 2) Olanzapine capsule 15 mg once/day and placebo CBD tablets twice/day; 3) Placebo CBD tablets twice/day and placebo olanzapine capsule once/day. Primary outcome measure is change in the Positive and Negative Syndrome Scale total score.

"Cannabidiol Treatment in Patients With Early Psychosis" NCT02504151
https://clinicaltrials.gov/ct2/show/NCT02504151?term=cannabis+schizophrenia&rank=34

This crossover trial is now recruiting patients and has an estimated completion date of October, 2018. An anticipated 72 adults will be recruited in Connecticut. Patients will be randomized into receive either: 1) treatment with CBD for four weeks followed by two week washout period, followed by four weeks of placebo or 2) placebo for four weeks, followed by a 2 week washout period, followed by four weeks of treatment with CBD. Primary outcome measures

are change in Positive and Negative Syndrome Scale and Clinical Global Impression of Severity scale.

Observational Studies

Study results presented in reviews of the involvement of the endocannabinoid system (ECS) in psychotic disorders leave little doubt of involvement. However, there is not yet clear understanding of the nature of that involvement. Something that is clearly emerging is the difference in action between THC and CBD, when it comes to the ECS and schizophrenia. Where THC causes acute psychotic effects even in some healthy persons and is implicated in precipitating psychotic disorders and exacerbating psychotic disease, CBD appears to be anti-psychotic, countering the pro-psychotic effects of THC. The presence of both THC and CBD in cannabis – in varying amounts, depending on strain, cultivation, and processing – might be at the heart of confusing scientific signals about the role of cannabis in psychotic disease. To go into the material in detail, the articles and resources discussed below are recommended as a starting point.

Information for Health Care Professionals: Cannabis and the cannabinoids. Health Canada. 2013. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/med/infoprof-eng.pdf

The "Schizophrenia and psychosis" section (pages 64-65) provides a concise, heavily-referenced discussion of what is known about the involvement of the endocannabinoid system in psychosis, the association of cannabis and THC with psychotic disease and the tantalizing evidence that CBD may have a therapeutic role. The report puts in bold its recommendation regarding whole-plant cannabis products and THC: "The findings presented above and in section 7.7.3 suggest that cannabis use, as well as exposure to Δ^9-THC alone, would not be beneficial, and in fact would actually be harmful to those who may be suffering from psychotic disorders, or who may have a genetic predisposition or family history of psychosis or schizophrenia." Regarding CBD: "The therapeutic potential of CBD alone in the treatment of schizophrenia/psychosis, while promising, requires further study."

Brief Review of Human Studies Regarding Increased Risk of Harm with Cannabis Use (May, 2016) Report produced by the Office of Medical Cannabis at the Minnesota Department of Health. http://www.health.state.mn.us/topics/cannabis/practitioners/humanstudies.pdf

The "Cannabis use and psychotic disorders" section (pages 9-12) provides a brief review of the large literature of studies investigating a potential causal or contributory role of cannabis use in bringing psychotic disorders on or making their outcomes worse. Though study findings regarding use of cannabis among persons with established psychotic disorders are not entirely consistent, most find an association between cannabis use and worse outcomes for at least some of the domains of symptoms. Nearly all the patients in the cited population studies were

using smoked cannabis purchased on the street. The cannabis consumed likely varied in amounts of THC, CBD, and other constituents – but presumably had the typical high levels of THC and low levels of CBD found in street marijuana.

Schubart CD, Somer IEC, Fusar-Poli P, de Witte L, Kahn RS, Boks MPM. Cannabidiol as a potential treatment for psychosis. *Eur Neuropsychopharm* 2014;24:51-64.

This article provides a comprehensive review of the categories of evidence for cannabidiol as a potential treatment for psychotic disorders. It includes evidence from: studies of the immune and endocannabinoid systems, animal studies, human experimental studies, imaging studies, epidemiologic studies, and clinical studies. This review concludes, "Evidence from several study domains suggests that CBD has some potential as an antipsychotic treatment. … Given the high tolerability and superior cost-effectiveness, CBD may prove to be an attractive alternative to current antipsychotic treatment, possibly in specific sub-groups of patients. However, to date the vast majority of the current evidence comes from experimental non-clinical studies and case reports. Although promising, this does not provide evidence that CBD has antipsychotic properties. Therefore, the only clinical evidence currently available for CBD as an antipsychotic agent is the relatively small (n=42) clinical trial published by Leweke et al. (2012). A large double blind randomized clinical trial in a new study population, comparing CBD to an atypical antipsychotic agent is required to truly advance the field. Moreover, illuminating pharmacological pathways through which CBD reduces the experience of psychotic symptoms could also lead to the design of new synthetic agents that act through the endocannabinoid system in ameliorating psychotic symptoms."

Iseger TA, Bossong MG. A systematic review of the antipsychotic properties of cannabidiol in humans. *Schizophrenia Research* 2015;162:153-161.

This systematic review focuses on studies of antipsychotic properties of cannabidiol (CBD) in humans. The paper discusses studies in four categories: the impact of CBD/THC ratios in cannabis on measures relevant for psychosis, 2) Neuropsychological studies with acute CBD administration to healthy volunteers, 3) Neuroimaging studies with acute CBD administration to healthy volunteers, 4) Studies with CBD administration to patients with psychotic symptoms. The paper concludes, "Results show the ability of CBD to counteract psychotic symptoms and cognitive impairment associated with cannabis use as well as with acute THC administration. In addition, CBD may lower the risk for developing psychosis that is related to cannabis use. These effects are possibly mediated by opposite effects of CBD and THC on brain activity patterns in key regions implicated in the pathophysiology of schizophrenia, such as the striatum, hippocampus and prefrontal cortex. The first small-scale clinical studies with CBD treatment of patients with psychotic symptoms further confirm the potential of CBD as an effective, safe and well-tolerated antipsychotic compound, although large randomized clinical trials will be needed before this novel therapy can be introduced into clinical practice.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of schizophrenia were found.

References

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