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POST MARKETING CLINICAL TRIAL TO EVALUATE THE SAFETY & EFFICACY OF CANNAEASE VIJAYA TINCTURES (SLEEP WELL 10%)

Vaidya (Dr.) Piyush Juneja, BAMS,.PDCR, PGCRCDM, MBA

Sponsor:

Ananta Hempworks Solutions Pvt. Ltd., A-112, First Floor, DDA Sheds, Okhla Phase II, New Delhi – 110020, India

Introduction

Cannabis has been used in traditional medicine since the Vedic ages. There is no complete ban on cannabis under the NDPS act in India as its scientific and medical uses is allowed under the law.

The effect of cannabis in healing insomnia is ambiguous and has been the subject of much debate. However, as per a recent meta-analysis by Bhagavan et al., there are data available to establish the positive effect of cannabis in treating people dealing with insomnia, but it is still poor in quality because of the short treatment period and little sample sizes 2.

In addition to chronic pain and mental health-related conditions, sleep disorders are one of the major reasons for which patients report using cannabis for medical purposes 3.

Sleep, which is a pivotal requirement for optimum health, involves various factors such as duration and quality 4. As per recent research, poor sleep timing and inconsistency in sleep are linked to hazardous health outcomes such as cardiovascular ailment and depression. 6-9.

Sleep problems like insomnia continue to be a major burden on society despite improvements in pharmaceutical therapy and psychotherapy. As medications for the management of insomnia, cannabinoids are gaining popularity and huge acceptance in the present time.

Often, patients report taking recreational or medical cannabis to get rid of primary sleep disorders 10 like insomnia or as a secondary treatment for other psychiatric and medical issues including anxiety, depression, chronic pain, fibromyalgia, etc. 11.

The most used pharmacologic treatments for insomnia and sleep disorders include benzodiazepines, H1-antagonists, and hypnotics (e.g., zopiclone, zolpidem, etc.). Several other drugs including second-generation antipsychotics and antidepressants (such as trazodone and mirtazapine) are used off-label to improve sleep efficacy in patients 12.

While these drugs help improve the sleep cycle, many of the medications may show unfavourable side effects including weight gain, daytime sleepiness, dizziness, cognitive impairment, metabolic syndromes and the possibility of addiction etc.

More than 120 distinct Phytocannabinoids have been identified in the cannabis flower, with a delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD) being the most extensively researched cannabinoids 12. Cannabis, particularly THCrich strains, is known to have a dose-dependent impact on sleep 13. THC interacts with the CB1 receptors in the brain, which causes it to have a biphasic effect on sleep 14. When administered in lower doses, THC can significantly decrease sleep latency and has also been linked to easier falling asleep, more slow wave sleep, and longer total sleep duration 15-17. At high potency THC dosages in cannabis, rapid eye movement (REM) sleep and REM density have been shown to decrease 18.

It has been demonstrated that CBD, the second most prevalent cannabinoid in cannabis, affects sleep latency in two different ways. While CBD, at lower doses, may have a stimulating effect but at greater concentrations, it might be more sedative. It can lengthen total sleep time and reduce the number of night-time awakenings. Overall, it can be said that cannabis may speed up the onset of sleep, which would enhance sleep quality.19

Studies suggest that THC and THC derivatives, used either alone or in conjunction with CBD, have been demonstrated to enhance self-reported sleep scores 20.

Due to the limitations of current pharmacologic therapy and the preliminary evidence from small-scale randomized controlled trials suggesting cannabis can treat sleep disorders, it is reasonable to review patients who use cannabis for sleep and evaluate their sleep scores as well as other indicators of improvement or negative effects of cannabis use.

Methods

The primary objective of this study was to examine significant improvement in the Insomnia Severity Index (ISI) and sleep logs of insomnia patients. The secondary objective is to record any adverse event and determine the nature of the adverse event after the administration of specified doses of medication.

Design

A Post Marketing, Open-Label Study.

Volunteers were screened at Visit 1 and eligible subjects were enrolled.

Visit 2 & 3 (final) were scheduled at 30 days & 60 Days of interval respectively. Safety tests were performed at visit 1 and end of visit 3. At the end of the study, the remaining IP was retrieved (as applicable) from the subject and measured. The difference between initial quantity and remaining quantity compared against the standard usage quantity. This was used to measure the compliance.

Inclusion/Exclusion Criteria (Patients & Recruitment)

Inclusion Criteria

- Provide informed consent prior to any study specific assessments being performed
- Between 18 and 60 years old, inclusively
- Insomnia as defined by an ISI score of 8 or above
- Insomnia symptoms for at least 3 months $< \text{ or } = 6.5$ hours of sleep per night Resident of India and currently living in the India for the duration of the trial

Exclusion Criteria

- Presence of an active and progressive physical ailment (e.g., acute pain, congestive- heart failure, Unstable medication schedule (change to dosage or timings within the past 3 months)
- Identification of a bipolar disorder, psychotic disorder, or other medical condition contraindicated by sleep restriction
- Have professional or family commitments that prevent them from following a typical sleep schedule, which is defined as going to bed between 8:00 pm and 2:00 am and waking up between 4:00 am and 10:00 am.
- Individuals who need to be vigilant or careful to prevent serious mishaps in their daily lives or at work. Examples include: Long-haul truck drivers, Long- distance bus drivers, Air traffic controllers, Operators of heavy machinery, some assembly line jobs.
- Pregnant or intending to get pregnant during the trial.
- Other untreated sleep disorders that the subject has self-reported (e.g., parasomnias, obstructive sleep apnoea, periodic leg movements)
- Took part in an investigational research study in the past 30 days.

Outcomes

The Primary Efficacy endpoints were Improvement in the Insomnia Severity Index (ISI) and sleep logs of insomnia patients. Secondary Endpoints Included assessing the duration of treatment effect after the end of treatment & to assess the safety and tolerability after 60 days of repeated doses.

Follow-Up

Patients were reviewed at 30 days & 60 days after starting medical cannabis. Site Staff under the supervision of the investigator conducted follow-up appointments with the patients to assist in medication counselling, side effects, dosing, and drug interactions. Patients were given a subject diary to complete the information accordingly.

Patients were given a form i.e. ISI at the time of enrolment and also at day 30 & day 60 visits the same were being reviewed. It included the Insomnia Severity Index, which was used to analyse baseline insomnia severity and the improvement accordingly, general questions like previously tried therapies, medical conditions, and impact on quality of life. ISI is a validated seven-item self-report with adequate psychometric properties that captures the nature, impact & severity of insomnia.²⁰ The score is interpreted as follows: absence of insomnia (0-7), sub-threshold insomnia (8-14), moderate insomnia (15-21), and severe insomnia (22-28).

Results

50 patients were reported to have sleep problems at the time of screening. Among these, 30 patients also had anxiety or stress-related disorders, 8 had IBS, 7 had PTSD, and the remaining 2 had psoriasis. (Table:1)

Table 1: Self-Reported diagnosed condition at the time of screening

Condition	n
Anxiety/Stress	30
Sleep Disorders	50
IBS	8
PTSD	7
Psoriasis	2

It was observed that only 12 individuals had used cannabis for medical purposes, whereas the rest 38 patients never tried cannabis (Table 2). Among the 50 patients, 32 were male and 18 were females (Table 3).

Table 2: History of Cannabis Administration

Previous Cannabis Use	12
Recreational Cannabis	0
Medical Cannabis	12
Cannabis Naïve (No Previous Cannabis use)	38

Table 3: Gender Distribution of Patients

Male	32
Females	18

As per the age group dissemination, 2 patients were between the age of 18 and 20, 6 patients belonged to the age group of 21-30, 19 participants were between the ages of 31 and 40, 18 patients belonged from the age group of 41 to 50, Rest 5 participants were between the ages of 51 and 60 years.

Table 4: Age (in Y:Years) Distribution of Patients

18-20 Y	2
21-30 Y	6
31-40 Y	19
41-50 Y	18
51-60 Y	5

Table 5 : Safety & Efficacy endpoints in patients using medical cannabis for sleep disorders (n=50)

Endpoint	n
Safety Endpoints	
No adverse effect reported	39
Mild adverse effects	11
Efficacy Endpoints	
Subjective Improvement in sleep with medical cannabis use	37
Very Significant Subjective improvement in Sleep	10
No Change in Sleep Disorder	3
Worsening Sleep Disorder	0

As per the data regarding safety endpoint, Among the 50 patients, 39 reported no serious effects while the remaining 11 individuals had mild adverse side effects.

Also the efficacy endpoints were being analysed and following results were being obtained:

37 patients reported subjective improvement in sleep with medical cannabis use. A very significant subjective improvement in sleep was observed in 10 patients. 3 individuals reported no change in sleep disorder. There was no report of worsening sleep disorder. (Table 5)

Discussion

Sleep-related health issues are one of the most common disorders indicated for medical cannabis usage. Our Study also showed that 94% of patients report a subjective improvement in their sleep.

Patients also reported anxiety and stress disorder along with sleep issues in our study. Anxiety can affect a patient's sleep. Several patients reported reduced anxiety at night which helped them sleep as well.

Adverse Events

Only 22% of patients reported any side effects, and those that they did report were moderate ones like nausea, mild diarrhoea, constipation, and acid reflux. None of them was intolerable.

Study Limitations

The current study has limitations because it only included 50 subjects for analysis and was an open-label post marketing study. To offer more information, large randomised controlled trials are required.

Conclusion

Our analysis of cannabis usage in patients with sleep issues reveals some significant benefits including subjective patient-reported improvement in insomnia.

This study provides some important new information about medical cannabis and sleep disorders.

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