Title of Research Project:

Examining the Efficacy of a Therapeutic Combination of Dronabinol (synthetic □9-tetrahydracannabinol) and Palmitoylethanolamide for Tourette Syndrome

NCT03066193

IRB Approval Date: 27 September 2017

YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2015-2)

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: Examining the Efficacy of a Therapeutic Combination of Dronabinol (synthetic Δ^9-tetrahydracannabinol) and Palmitoylethanolamide for Tourette Syndrome			
Principal Investigator: Michael H. Bloch, MD, MS	**Yale Academic Appointment:** Associate Professor		
Department: Child Study Center			
Campus Address: 230 South Frontage Rd., New Haven, CT 06520 NIHB-205			
Campus Phone: 203-745-9921	**Fax:** 203-785-7611	**Pager:** 203-745-9921	**E-mail:** Michael.bloch@yale.edu
Protocol Correspondent Name & Address (*if different than PI*): Angeli Landeros-Weisenberger, MD, 230 South Frontage Rd, New Haven, CT 06520 SHM-I-371			
Campus Phone: 203-737-4809	**Fax:** 203-737-5104	**E-mail:** angeli.landeros@yale.edu	
Yale Cancer Center CTO Protocol Correspondent Name & Address (*if applicable*):			
Campus Phone:	**Fax:**	**E-mail:**	
Business Manager:			
Campus Phone :	**Fax :**	**E-mail**	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☒ **NA**			**tment:**
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

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See Disclosures and Management of Personal Interests in Human Research
http://www.yale.edu/hrpp/policies/index.html#COI

Yes • No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

Yes • No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as co-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: http://www.yale.edu/coi/

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

- ☐ Magnetic Resonance Research Center (MR-TAC)
- ☐ Yale Cancer Center/Clinical Trials Office (CTO)
- ☐ Yale Cancer Center/Smilow
- ☐ Yale-New Haven Hospital
- ☐ Cancer Data Repository/Tumor Registry
- ☐ Yale University PET Center
- ☐ YCCI/Church Street Research Unit (CSRU)
- ☐ YCCI/Hospital Research Unit (HRU)
- ☐ YCCI/Keck Laboratories
- ☐ Yale-New Haven Hospital—Saint Raphael Campus
- ☒ Specify Other Yale Location: Yale Child Study Center

b. External Location[s]:

- ☐ APT Foundation, Inc.
- ☒ Connecticut Mental Health Center
- ☒ Clinical Neuroscience Research Unit (CNRU)
- ☐ Other Locations, Specify:
- ☐ Haskins Laboratories
- ☐ John B. Pierce Laboratory, Inc.
- ☐ Veterans Affairs Hospital, West Haven
- ☐ International Research Site

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(Specify location(s)):

c. Additional Required Documents *(check all that apply)*: ☒ N/A

☐ *YCCI-Scientific and Safety Committee (YCCI-SSC) Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC) Approval Date:
☐ *YCC Protocol Review Committee (YRC-PRC) Approval Date:
☐ *Dept. of Veterans Affairs, West Haven VA HSS Approval Date:
☐ *Radioactive Drug Research Committee (RDRC) Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC) Approval Date:
☐ Yale University RSC (YU-RSC) Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC) Approval Date:
☐ *Nursing Research Committee Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR) Approval Date:
☐ Dept. of Lab Medicine request for services or specimens form
☐ Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx)

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

   3 years

3. **Research Type/Phase: (Check all that apply)**
   a. **Study Type**
   ☒ Single Center Study
   ☐ Multi-Center Study
   Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☐
   ☐ Coordinating Center/Data Management
   ☐ Other:

   b. **Study Phase** ☐ **N/A**
   ☐ Pilot ☐ Phase I ☒ Phase II ☐ Phase III ☐ Phase IV
   ☐ Other (*Specify)*

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☒ Clinical Research: Patient-Oriented
☐ Clinical Research: Epidemiologic and Behavioral
☐ Translational Research #1 ("Bench-to-Bedside")
☐ Translational Research #2 ("Bedside-to-Community")
☐ Clinical Research: Outcomes and Health Services
☐ Interdisciplinary Research
☐ Community-Based Research

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5. Is this study a clinical trial? Yes ☒ No ☐

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"

If yes, where is it registered?

Clinical Trials.gov registry ☒

Other (*Specify*)

*Registration of clinical trials **at their initiation** is required by the FDA, NIH and by the ICMJE.*

If this study is registered on clinicaltrials.gov, there is new language in the consent form and compound authorization that should be used.

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, http://ycci.yale.edu/researchers/ors/registerstudy.aspx or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)? Yes ☒ No☐

7. Will this study have a billable service? *A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects*.

Yes ☐ No☒

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

8.. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes____No X *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

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a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform?
b. Will you be using any new equipment or equipment that you have not used in the past for this procedure?

c. Will a novel approach using existing equipment be applied?

If you answered "no" to question 8a, or "yes" to question 8b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. ***By signing this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH****.*

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply. Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

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PI	Title of Grant	Name of Funding Source	unding	unding Mechanism
Michael H. Bloch, MD, MS	Examining the Efficacy of a Therapeutic Combination of Dronabinol (synthetic Δ^9-tetrahydracannabinol) and Palmitoylethanolamide for Adults with Tourette Syndrome	Therapix Biosciences Ltd.	Federal ☐ State ☐ Non Profit ☒ Industry ☐ Other For I rofit Other	Grant-M# ☐ Contract# ☐ Contract Pending ☒ Investigator/Department Initiated ☐ Sponsor Initiated Other, Specify:
			Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For I rofit Other	Grant-M# ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated Other, Specify:
			Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For I rofit Other	Grant-M# ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated Other, Specify:

IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. ***Note: the PI's home department will be billed if this information is not provided.***

Send IRB Review Fee Invoice To:

Name: Dr. Adi Zuloff-Shani, PhD
Company: Therapix Biosciences Ltd.
Address: 5 Azrieli Center (Square Tower) 27 Fl., Tel-Aviv 6702501, Israel

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

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NOTE: The HIC will remove from the protocol any personnel who have not completed required training.

	Name	Affiliation: Yale/Other Institution (Identify)	NetID
Principal Investigator	Michael H. Bloch, MD, MS	Yale	MHB32
Role: Co-Investigator	James F. Leckman, MD	Yale	JFL2
Role: Co-Investigator	Angeli Landeros-Weisenberger, MD	Yale	ALW495
Role: Study Personnel	Jessica A. Johnson, BS	Yale	JAJ62
Role: Study Personnel	Shilpa Telang, M.D.	Yale	SB2558
Role: Study Personnel	Baris Olten, M.D.	Yale	BO222

A personnel protocol amendment will need to be submitted when training is completed.

SECTION IV: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

_Michael H. Bloch, MD, MS_____ 10/06/16

PI Name (PRINT) and Signature Date

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As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set forth by the University and qualify to serve as the faculty advisor of this project.
- I assume all of the roles and responsibilities of a Principal Investigator even though the student may be called a PI.

_____ _____

Advisor Name (PRINT) and Signature Date

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)
☐ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)
☐ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

_____ _____

Chair Name (PRINT) and Signature Date

_____

Department

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YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

YNHH HSPA Name (PRINT) and Signature _____ Date _____

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

This is an investigator-initiated proof of concept study with the purpose to examine the safety, tolerability and feasibility of Dronabinol (synthetic Δ^9-THC) and PEA for the treatment of adults with Tourette syndrome.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Tourette syndrome (TS) affects slightly less than 1% of school-age children and 0.5% adults.(1) The tics associated with TS can have significant effects on the academic and social development of children as well as affecting their overall self-esteem and mental health. Although the majority of children experience a decrease in their tics during adolescence, the worst symptoms are usually experienced by adults with intractable TS.(2, 3)

There are significant limitations to the available treatments for TS in terms of both efficacy and side-effects. Currently, two antipsychotic agents are the only FDA-approved medications for TS: haloperidol and pimozide. Atypical antipsychotic agents are also widely utilized in the treatment of TS even though only risperidone has demonstrated efficacy in multiple, placebo-controlled clinical trials.(4-6) Antipsychotic agents, although the most effective agent in reducing tics, are not utilized as a first-line treatment for tics (especially in children) because of the significant side-effects associated with their use.(4-6) New treatments for TS are urgently needed.

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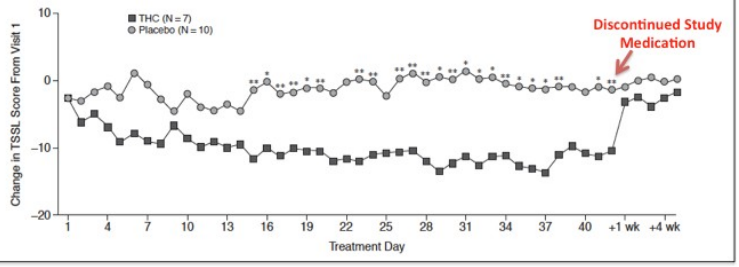
Several lines of evidence suggest that cannabis (Cannabis *sativa*) and Δ^9-tetrahydracannabinol (Δ^9-THC) may be effective in the treatment of tic disorders. Anecdotal case reports have long suggested that smoking marijuana may improve tic symptoms.(7-9) Standardized interviews of 64 consecutive TS patients seeking treatment in Germany reported that 82% of TS patients experienced a reduction or complete remission of tic symptoms when smoking cannabis.(10) Δ^9-tetrahydracannabinol (Δ^9-THC), the principal active constituent of cannabis has been studied in randomized, placebo-controlled trials in TS.(10) A double-blind, placebo-controlled crossover trial of 5-10mg of Δ^9-THC in 12 adults with TS, demonstrated a significant reduction in measures of tic severity and global improvement with Δ^9-THC compared to placebo. Tourette syndrome Symptom List (TSSL) ratings of tic severity were significantly reduced when subjects were given Δ^9-THC (12.5±11.0 point) compared to placebo (2.5±7.0 points) (p=0.015).(11) A 6-week, double-blind, placebo-controlled trial of 24 adults with TS also demonstrated a significant benefit of Δ^9-THC compared to placebo. Figure 1 depicts the change in TSSL scores during the course of the 6-week trial. Subjects randomly assigned to Δ^9-THC experienced significant reduction of their tic symptoms compared to placebo after the first 2 weeks of treatments that continued throughout the 6-week trial. These improvements vanished when subjects discontinued Δ^9-THC.(12) The treatment effect size observed for Δ^9-THC was considerably larger than that observed in placebo-controlled trials of currently available treatments for TS.

Figure 1: Change in Tic Severity in Placebo-Controlled Δ^9-THC trial of 24 Adults with TS.



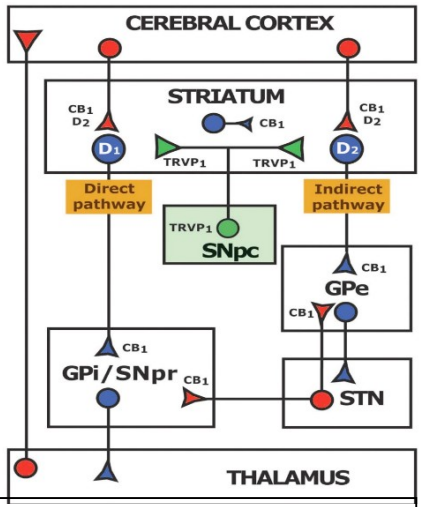


Figure 2: Diagram of CB_1 role in Dopaminergic Motor Circuits of Basal Ganglia. GABAergic inhibitory pathways are represented in blue and glutamatergic excitatory pathways in red. Modulatory dopaminergic connections are indicated in green. CB_1, cannabinoid receptor type 1; $TRPV_1$, transient receptor potential vanilloid type 1; D_1, dopaminergic receptor type 1; D_2, dopaminergic receptor type 2; GPe, *external globus pallidus*; GPi, *internal globus pallidus*; STN, *subthalamic nucleus*; SNpc, *substantia nigra pars compacta*; SNpr, *substantia nigra pars reticulata*. [13]

CB1 receptors may be involved in the pathophysiology of TS: Biological evidence also suggests that the brain cannabinoid system may contribute to the pathophysiology of TS and other movement disorders.(13, 14) CB1 receptors and endocannabinoids are highly expressed in the basal ganglia and appear to have an important role in modulating dopaminergic motor circuits.(14) Specifically CB1 receptors are expressed presynaptically on medium-spiny neurons -- striatal neurons projecting in both the direct (substantia nigra pars reticulata and the globus pallidus pars interna) and indirect (globus pallidus pars externa) pathways.(15) Activation of CB1 receptors in combination with D1 receptors of the direct pathway serves to decrease adenyl cyclase release within projection neurons. By contrast, activation of CB1 receptors in combination with D2 receptors serves to stimulate adenyl cyclase in projection neurons of the indirect pathway.(14) Figure 2 illustrates the mechanisms by which endocannabinoids play an important role in motor inhibition. Although CB1 receptors are not expressed by most striatal GABAergic interneurons, CB1 receptors are expressed by parvalbumin positive interneurons and some cholinergic interneurons.(15) Parvalbumin positive and cholinergic striatal interneurons have been demonstrated to be significantly reduced in post mortem studies of TS patients.(16)

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The major limitations of both cannabis and dronabinol use, is the adverse psychoactive side effects, they induce in higher doses. The psychoactive effects of Δ^9-THC are primarily mediated by its activation of CB1G-protein coupled receptors, which result in a decrease in the concentration of the second messenger molecule cAMP through inhibition of adenylate cyclase (3). Thus, in order to harness the therapeutic potential of Δ^9-THC for patients with Tourette's syndrome, there is a need to reduce the accompanied adverse effects.

We hope to use the entourage effect to deliver the therapeutic benefits of Dronabinol (synthetic Δ^9-THC) in reducing tics with decreased psychoactive effects using Palmitoylethanolamide (PEA). The basic idea of the entourage effect is that cannabinoids within the cannabis plant work together, or possess synergy, and affect the body in a mechanism similar to the body's own endocannabinoid system. Palmitoylethanolamide (PEA) is a lipid messenger known to mimic several endocannabinoid-driven activities although it does not bind the classical CB receptors. Based on an activity enhancement of other physiological compounds, by potentiating their affinity for a receptor or by inhibiting their metabolic degradation, PEA may indirectly stimulate the effects of both phyto- or endocannabinoids, either by its role as an agonist of the transient receptor potential vanilloid type 1 (TRPV1), peroxisome proliferator-activated receptor-α (PPAR-α) and the cannabinoid receptors(6). PEA capacity to exert 'entourage effects' is derived from its ability to affect multiple targets within the body, to improve the absorption of active ingredients and to minimize adverse side effects (7).

One of the most important compounds to be affected by PEA is endocannabinoid anandamide (AEA). Sub-effective dose of AEA, when co-injected with PEA, significantly decreases blood pressure. PEA also enhances the hypotensive responses to both AEA and meth AEA (8). AEA induces vasorelaxation only in the presence of PEA, and the PEA potentiating occurs through TRPV1 receptors. The discovery of anandamide came from research into CB1 and CB2, as it was inevitable that a naturally occurring (endogenous) chemical would be found to affect these receptors. As PEA potentiate the effect of AEA, it is plausible to assume it may exert the same effect on cannabis derived phytocannabinoids such as Δ^9-THC. In a murine model of behavioral and pain perception it was shown that addition of PEA to THC reduced the deleterious behavioural side effects of THC and potentiate the analgesic effect of THC sub-effective dose (Brener et al, 26th symposium of the ICRS, 2016)

PEA has been shown to possess anti-craving effects in cannabis dependent patients, is efficacious in the treatment of withdrawal symptoms, produces a reduction of cannabis consumption and is effective in the prevention of cannabis induced neurotoxicity and neuro-psychiatric disorders. Moreover, by combining Δ^9-THC therapy with PEA, one can overcome the over-sensitization/irritation that the Δ^9-THC alone causes to the respiratory tract, by PEA ability to stabilize mucosal mast cells and prevent their degranulation. Thus combination of Δ^9-THC with PEA, may be proved to be by far more safe and effective than Δ^9-THC alone.

Dronabinol:

Dronabinol is a cannabinoid designated chemically as (6aR-trans)6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol. CAS registry number 1972-08-03.
Dronabinol is the INN for a pure isomer of THC, (-)-trans-Δ9-tetrahydrocannabinol and is the active ingredient in dronabinol capsules, is synthetic delta-9tetrahydrocannabinol (delta-9-THC). Delta-9-tetrahydrocannabinol is also a naturally occurring component of Cannabis sativa L. (Marijuana).
Synthesized dronabinol is marketed as Marinol (a registered trademark of Solvay Pharmaceuticals). Dronabinol is also marketed, sold and distributed by PAR Pharmaceutical Companies under the terms of a license and distribution agreement with SVC pharma LP, an affiliate of Rhodes Technologies.
. Δ^9-THC is the primary psychoactive component of the Cannabis plant, and is the most notable cannabinoid. Δ^9-THC possesses activities as a psychoactive agent, analgesic, muscle relaxant, antispasmodic, bronchodilator, neuroprotective antioxidant and antipruritic agent.

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Δ^9-THC has affinity to both CB1 and CB2 classical cannabinoid receptors. Classical cannabinoid receptors (CB1 and CB2) are 7 transmembrane G-protein couple receptors (known as GPCRs) negatively coupled to adenylyl cyclase and positively coupled to MAPKs such as extracellular signal related kinases 1 and 2 (ERK1/2) through Gi/o proteins (17). CB1 is highly expressed in neurons within the hippocampus, basal ganglia, cerebellum, cortex, thalamus and periaqueductal gray but poorly expressed in the respiratory center of the brainstem, hence the reason for lack of respiratory depression seen with cannabis toxicity. CB2 is expressed on immunocytes including microglia and mast cells. CB2 is poorly expressed in the CNS (100-fold lower expression than CB1) but rapidly upregulated in microglia and neurons with neural injury and inflammation (18).

In the United States, Marinol is a Schedule III drug, available by prescription, considered to be non-narcotic and to have a low risk of physical or mental dependence. Marinol has been approved in US and in Canada in the treatment of anorexia in AIDS patients (19-21), as well as for refractory nausea and vomiting of patients undergoing chemotherapy 19,22,24). It was proved as safe and effective for these uses (19).

Nabiximols (Sativex) is a combination of Cannabidiol (CBD) and THC (at a ratio of 1:1). This product was approved in Canada as a mouth spray to alleviate neuropathic pain, spasticity, overactive bladder, and other symptoms of multiple sclerosis. This product is also approved in additional countries in Europe (including UK) as well as Israel.

Δ^9-THC was investigated in additional clinical studies evaluating its use in a variety of clinical indications other than the approved ones (see Appendix 1) (20-22). These include evaluation of Δ^9-THC efficacy on pain reduction in different patient's populations (multiple sclerosis (23), amyotrophic lateral sclerosis (ALS) (24), fibromyalgia (25), cancer, abdominal hysterectomy (26), headaches (27), spinal cord injury, and muscle spasticity), obstructive sleep apnea (28), internal pressure in end-stage open-angle glaucoma (29, 30), dementia-related neuropsychiatric symptoms (NPS), progressive inflammatory brain disease, antiemetic effect, colonic motility and sensation.

In MS patients, the effect of Δ^9-THC on various symptoms (such as muscle spasticity, illness progression, and urge incontinent episodes) was also investigated in different clinical trials. In cancer patients, the effects of Δ^9-THC on chemosensory alterations, appetite, quality of life and anorexia were also investigated. Side-effects associated with Δ^9-THC include mood changes, dizziness, drowsiness, confusion, trouble concentrating, feeling "high," warmth or tingly feeling, an exaggerated sense of well-being, anxiety, lightheadedness, headache, red eyes, dry mouth, nausea, vomiting, stomach pain, diarrhea, sleep problems (insomnia), clumsiness, lack of coordination, weakness, unsteadiness or insomnia. Serious, uncommon side-effects associated with Δ^9-THC include seizure, paranoia, disorganized/unusual behavior and tachycardia.(31)

<u>PEA</u>:

PEA is a primary fatty acid amide found in egg yolk, and as such, it falls under the definition of "egg yolk-derived phospholipids" (As an ingredient in term and preterm infant formula), which are listed as GRAS ingredients (GRN No. 411). Furthermore, PEA can be considered as a derivate of fatty acid ethyl ester (from anchovy or menhaden oil), which are listed as GRAS ingredient (GRN No. 494).

PEA content can also be attributed to FDA List of Indirect Additives Used in Food Contact Substances under general Main Term: ANIMAL OIL FATTY ACID AMIDES, Doc No. 7625, CAS RN 977139-08-4. In addition, PEA is listed under the Code of Federal Regulations Title 21, 21CFR175.105 (Revised as of April 1, 2014) SUBCHAPTER B--FOOD FOR HUMAN CONSUMPTION PART 175 -- INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS.

In Europe, PEAPure is categorized as food supplement and marketed as such. Other PEA derived products (Normast® and Pelvilen®) are approved via a decentralized procedure in few EU countries (Italy, Spain, Slovakia, Germany and the Netherlands) as a food for medical purposes.

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

An additional PEA product (Palmidrol) has been approved nationally in Spain and Italy as an anti-inflammatory agent (CAS 0000544-31-0).
Clinical research on PEA started in the 1960s and 1970s, especially in the Czech Republic. PEA, at that time under the brand name 'Impulsin' was indicated for prevention of flu and respiratory diseases and immune system enhancement (32-36). In general, PEA has been shown to be effective, tolerable and safe. PEA has been submitted for clinical relevancy as an analgesic, as a treatment for various chronic pain states. More than 30 various clinical trials have been conducted, shedding light on clinical relevance of PEA as a standalone agent or as a part of combinational therapy. It is of high importance that these trials demonstrate no relevant side-effects and no drug-drug interactions, when PEA has been administered. Full range of PEA doses had been implemented, most notably 300 mg or 600 mg for up to two times a day (1200 mg/day) and up to two months. PEA has been found to be effective in many pain states. Clinically addressed pain states include refractory neuropathic pain, temporomandibular joint disorder (TMJD), Costen syndrome, pains due to lumbosciatic problems, low back pain, diabetes-induced carpal tunnel syndrome, entrapment neuropathy (with significant improvement in neurophysiological parameters (distal motor latency)).

When used in combination with other agents, such as Pregabalin (Lyrica, Pfizer), classical NSAIDs, transpolydatin or oxycodone, PEA has been found to potentiate the analgesic effect of the mentioned drugs. Efficacy of PEA as part of multimodal analgesic therapy in patients with low back pain has been demonstrated. PEA enhances the analgesic effects of other compounds. Visual, analog scale (VAS) is a psychometric response scale which can be used in questionnaires, has been found to lower from 7 to mean 2.5 in most cases of PEA use. All neurophysiological parameters improved on PEA. In patients suffering from MS and neuropathic pain and treated with PEA 300 mg twice daily, 14 of 20 patients were full responders. Significant decrease of spasticity (as measured via modified Ashworth scale) and pain after stroke due to treatment with PEA was also observed. PEA improves pain and nerve function in patients suffering from chemotherapy induced neuropathy. Pain significantly decreased and nerve function, as measured by laser evoked LEP, increased significantly. In 20 patients undergoing thalidomide and bortezomib treatment for multiple myeloma, changes in neurophysiological measures indicate that PEA exerted a positive action on myelinated fiber groups. PEA, possibly by moderating mast cell hyperactivity, relieved conduction blocks secondary to endoneural edema. In a severe condition such as painful neuropathy associated with multiple myeloma and chemotherapy, a safe substance such as PEA provides significant restoration of nerve function. In glaucoma patients, PEA effects have been investigated on intraocular pressure (IOP) in primary open angle glaucoma (POAG) and ocular hypertension (OH). Systemic administration of PEA reduces IOP in patients with glaucoma and ocular hypertension. PEA could be a valuable tool for the treatment of glaucoma.

Moreover, PEA based topical treatment for conditions such as atopic eczema, atopic dermatitis, contact allergic dermatitis, facial post-herpetic neuralgia and pruritus have shown to be an effective remedy. PEA based creams inhibit ultraviolet light-induced inflammation and DNA damage in human skin. PEA as an analgesic can be utilized in dentistry and has been used in study for Impacted Lower Third Molar Surgery. Administering PEA improves the postoperative course—in terms of pain—after lower third molar extraction.

Thus, PEA treatments by means of oral (systemic) or topical administration prove to be effective and safe, with no observable side effects, and no noticed drug-drug interactions. Appendix 2 provides a comprehensive list of previous trials conducted using PEA. In these trials no adverse events have been reported that exceed the rate observed with placebo controls.

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

Overview

We propose a 12-week, investigator-initiated, open-label trial of a therapeutic combination of Dronabinol and PEA in 18 adults with Tourette syndrome. Subjects will receive Dronabinol and PEA in combination for the duration of the trial. Our goal for this pilot study is to (1) provide initial safety, feasibility and tolerability data on both Dronabinol and PEA in a TS population and (2) provide data in order to make a more informed decision regarding the appropriate sample size and design of a larger clinical trial to prove efficacy (i.e. sample size and trial duration in large efficacy trial of the Dronabinol/PEA combination in TS).

Subjects

Eighteen adults will be recruited through the TS/OCD Clinic at the Yale Child Study Center. The Yale Child Study Center has a nearly three-decade history of successfully recruiting for pharmacological trials of TS. We will additionally recruit through email blast through local TS chapters and by contacting local providers who treat adults with TS. We will additionally contact adult subjects who recently completed other treatment trials for TS at our site and agreed to be contacted for future trials. Subjects will be compensated $500 for their participation.

Interventions

Subjects will be titrated up on Dronabinol dose during the first week of the trial (2.5mg Dronabinol for 3 days and then 5mg Dronabinol for 4 days increasing to 10mg Dronabinol for the remainder of the trial). Dronabinol will only be increased to 10mg at the week 1 assessment if the subject is tolerating the 5mg dose of Dronabinol and the Dronabinol may be reduced based on patient side-effects. Subjects will be assigned to receive two 400mg tablets of PEA daily for all 12 weeks. See pages 9-12 of this application for a detailed description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks for both Dronabinol and PEA.

Assessments

Pre-study screening procedure: After an initial phone screen to rule out obvious exclusions from the study protocol, potential subjects will have an initial evaluation that will be performed by a multidisciplinary clinical team. In addition to a standard clinical evaluation consisting of history, and mental status exam, subjects will receive a clinical diagnostic interview using the Structured Clinical Interview of DSM-IV (SCID). Additional rating scales will assess severity of tic symptoms and common comorbid symptoms such as OCD, ADHD, depression and anxiety severity which are listed below.

Baseline Assessments	Medical Assessments	Rating scales	
SCID	Vital Signs, ECG	YGTSS	PUTS
Psychiatric History	Physical Exam	Y-BOCS	Connors
General Medical History	Mental Status Exam	HAM-D	HAM-A
Chart review of Med Hx	Baseline Labs	CGI	AERS
	Urine Tox and Preg.	TSSL	

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

Outcome Measures:

- Improvement in Tic Severity -- Yale Global Tic Severity Scale (YGTSS) (Total Tic Score)
- Improvement of Premonitory Urges -- Premonitory Urge for Tics Scale (PUTS)
- Self-Report of Tic Severity – Tourette Syndrome Symptom List (TSSL)
- OCD Severity -- Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)
- ADHD severity -- Connors Adult Attention Deficit Hyperactivity Rating Scale (Connors)
- Depression Severity-- Hamilton Rating Scale for Depression (HAM-D)
- Anxiety Severity -- Hamilton Rating Scale for Anxiety (HAM-A)
- Overall Improvement -- Clinical Global Improvement Scale (CGI)
- Adverse Effects -- Adverse Events Rating Scale (AERS)

Safety Assessments:

A medical assessment including vital signs, ECG, physical exam, routine blood tests indicating physical health and urine drug screen and pregnancy test will be completed prior to study enrollment. These safety assessments will be repeated every 2 weeks throughout the trial. Additionally, subjects will be assessed for any adverse effects of medication using the adverse events rating scale at every study visit.

Within Trial Assessment Procedure:

The table below indicates the clinical ratings scheduled planned for the trial. Subjects will be evaluated every week during the course of the trial. Clinical ratings of symptom severity will be performed by a research investigator. A study physician will review laboratory values, assess medication side effects and assess study medication compliance.

				Study Week							Open Extension
	Measure	**Screening**	**Baseline**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**Every 4 Weeks**
Tic Severity	Yale Global Tic Severity Scale	X	X	X	X	X	X	X	X	X	X
	Premonitory Urge Scale	X	X	X	X	X	X	X	X	X	X
	Tourette Syndrome Severity List	X	X	X	X	X	X	X	X	X	X
Severity of Common Comorbid Disorders	Yale-Brown Obsessive-Compulsive Scale	X	X		X	X	X	X	X	X	X
	Connors ADHD Rating Scale		X		X	X	X	X	X	X	X
	Hamilton Depression Scale		X		X	X	X	X	X	X	X
	Hamilton Anxiety Scale		X		X	X	X	X	X	X	X
	Clinician-Rated Global Improvement		X	X	X	X	X	X	X	X	X
Psychiatric Assesment	SCID	X									
	Psychiatric Medication History	X									
	Mental Status Exam	X									
Medical Assesment	Medical History	X									
	Current Medication List	X	X								
	Physical Exam	X	X			X		X		X	X
	12 Lead ECG	X	X		X	X	X	X	X	X	X
	Vital Signs	X	X		X	X	X	X	X	X	X
Safety	Adverse Events Rating Scale		X	X	X	X	X	X	X	X	X
	Urine Toxicology	X		X	X	X	X	X	X	X	X
	Urine Pregnancy	X									
	Electrolytes	X			X	X	X	X	X	X	X
	LFTs	X			X	X	X	X	X	X	X
	PT/PTT	X			X	X	X	X	X	X	X
	BUN/Cr	X			X	X	X	X	X	X	X
Compliance	Pill Counts				X	X		X		X	X
				Assignment to THC/PEA combination for 12 weeks. Subjects will receive 2.3mgTHC/ 518mg PEA for 3 days then 5mg THC/ 518mg PEA 3 days and then 10mg THC/518mg PEA for the remainder of the 10 week trial.							10mg THC/518mg PEA for an additional 24 Weeks.

Extension Phase:

Subjects who report an improvement in the initial 12-week trial will be allowed to continue on the study medication (Dronabinol/PEA combination) free of charge for 6 months as long as they continue to complete clinical assessments every 4 weeks and test positive for cannabis on urine toxicology screen (indicating

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

compliance with study medication). They will be compensated $25 for each follow-up assessment at the conclusion of their participation in the trial.

Feasibility
James Leckman and the Yale Child Study Center have nearly a three-decade history of successfully recruiting for pharmacological studies of Tourette syndrome.(37-39) We have recently completed a 10-subject, uncontrolled trial of EPI-743, in the treatment of adults with Tourette syndrome. We also had been recruiting successfully for a placebo-controlled crossover trial of a Fatty acid amide hydrolase (FAAH)-inhibitor before it was placed on hold due to clinical concerns with these medications as a class (NCT02134080). The inclusion/exclusion criteria are extremely similar between the two trials and thus we suspect a large proportion of the subjects completing the EPI-743 and FAAH-inhibitor studies to be eligible to enroll in the current trial. Based on this large number of prevalent, research-interested patients we expect to meet recruitment goals for the current trial.

4. Genetic Testing N/A ☒

A. Describe
   i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned
   ii. the plan for the collection of material or the conditions under which material will be received
   iii. the types of information about the donor/individual contributors that will be entered into a database
   iv. the methods to uphold confidentiality

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?
C. Is widespread sharing of materials planned?
D. When and under what conditions will materials be stripped of all identifiers?
E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?
   i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?

F. Describe the provisions for protection of participant privacy
G. Describe the methods for the security of storage and sharing of materials

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

The subject population will include adults with significant tic symptoms that have not previously responded to evidence-based treatments for TS. Subjects will include interested patients from the TS/OCD clinic, as well as eligible subjects who respond to the clinicaltrials.gov website posting. Additionally, subjects will be recruited via email blast through local TS chapters and by contacting local providers who treat adults with TS. Furthermore, contact will be made with adult subjects who have recently completed other treatment trials for TS at the clinic and agreed to be contacted for future trials.

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

6. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ Children	☐ Healthy	☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
☐ Yale Students	☒ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion Criteria:

- Adult between 18-60 years of age
- Meet DSM-5 criteria for the diagnosis of Tourette syndrome
- Significant current tic symptoms: YGTSS total tic score greater than or equal to 22 at baseline
- On stable psychiatric medication regimen for a minimum of 4 weeks prior to beginning the trial
- Accepted method of birth control

Exclusion Criteria:

- Comorbid bipolar disorder, psychotic disorder, substance use disorder, developmental disorder or intellectual disability (IQ<70)
- Recent change (less than 4 weeks) in other medications that have potential effects on tic severity (such as alpha-2 agonists (guanfacine, clonidine or prazosin), SSRIs, clomipramine, naltrexone, lithium, anxiolytics, topiramate, baclofen etc.). Medication change is defined to include dose changes or medication discontinuation.
- Recent change in behavioral treatment for Tourette syndrome or comorbid conditions (i.e. OCD) within the last 4 weeks or initiation of behavioral therapy for tics within the last 12 weeks.
- Taking any co-medications (over the counter or prescription), food supplements/additives which can have a drug interaction with dronabinol or PEA.
- Positive pregnancy test or drug screening test
- History of cannabis dependence
- Significant Medical Comorbidity
- History of hypersensitivity to any cannabinoid or sesame oil

8. How will **eligibility** be determined, and by whom?

Subjects will first undergo a phone screen to initially determine eligibility. Information collected during the phone screen will be used only in the event that the subject continues to participate in the study.

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

After determining initial eligibility, research staff will provide a brief description of the research and the subject will undergo the screening procedures described previously. Once all screening procedures have commenced, research staff, along with the principal investigator, will review all relevant information and determine, based on the inclusion and exclusion criteria, if the subject is eligible to complete the remaining study procedures.

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

A medical assessment including vital signs, ECG, physical exam, routine blood tests indicating physical health and urine drug screen and pregnancy test will be completed prior to study enrollment. These safety assessments will be repeated every 2 weeks throughout the trial. Additionally, subjects will be assessed for any adverse effects of medication using the adverse events rating scale at every study visit.

The risks associated with the study include those related to: 1) screening, 2) phlebotomy, 3) Dronabinol and 4) confidentiality.

Note In previous trials involving PEA, no adverse events have been reported that have exceeded the rate observed with placebo controls. The absence of serious side effects or drug-drug interactions have been recorded is most likely due to the fact that PEA is an endogenous modulator in various foods such as eggs and milk.

1) Screening
   All subjects will undergo a Structured Clinical Interview for DSM-IV conducted by a research assistant, as well as a psychiatric evaluation by the principal investigator or one of the co-investigators. The diagnostic interviews may cover issues which are stressful to a person, for example, questions regarding the experience of paranoid thoughts or social isolation.
2) Phlebotomy
   A medical assessment including vital signs, ECG, physical exam, routine blood tests indicating physical health and urine drug screen and pregnancy test will be completed prior to study enrollment. Bruising, infection and thrombosis are all possible consequences of phlebotomy. The medical assessments will occur every two weeks during the 12-week trial. A total of approximately 3 tbsp of blood will be drawn over this time period, an amount which is well within the Red Cross blood standards.

3) Dronabinol (synthetic Δ^9THC)
   In various studies investigating Δ^9THC in the treatment of patients with AIDS and/or cancer, Δ^9THC has been co-administered with a variety of mediations (e.g., cytotoxic agents, anti-infective agents, sedatives, or opioid analgesics) without resulting in any clinically significant drug/drug interactions. However, it is possible Δ^9THC may interact with other mediations through metabolic and/or pharmacodynamics mechanisms. Additionally, potential added central nervous system depression may occur if Δ^9THC is used in combination with alcohol or other CNS depressants. Dronabinol is abusable and controlled [Schedule III (CIII)] under the Controlled Substance Act. Psychological and

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

physiological dependence have been noted in healthy individuals receiving Δ^9THC, however addiction is uncommon and has only been seen after prolonged high dose administration. In clinical trials with Δ^9THC in patients with AIDS, no abuse, diversion or systemic change in personality or social functioning were observed despite the inclusion of a substantial number of patients with a past history of drug abuse. Side-effects associated with Δ^9THC include mood changes, dizziness, drowsiness, confusion, trouble concentrating, feeling "high," warmth or tingly feeling, an exaggerated sense of well-being, anxiety, lightheadedness, headache, red eyes, dry mouth, nausea, vomiting, stomach pain, diarrhea, sleep problems (insomnia), clumsiness, lack of coordination, weakness or, unsteadiness. Serious, uncommon side-effects associated with Δ^9-THC include seizure, paranoia, disorganized/unusual behavior and tachycardia. Previous studies have shown that PEA is effective in the prevention of cannabis (a substance containing Δ^9THC) induced neurotoxicity and neuro-psychiatric disorders. Furthermore, the ability of PEA to stabilize mucosal mast cells and prevent their degranulation allows one to overcome the over-sensitization/irritation that the Δ^9THC alone causes to the respiratory tract. Thus the combination of Δ^9THC with PEA may be prove to be more safe and effective than Δ^9THC alone. Currently, approval has been granted from the FDA for the use of Δ^9THC in the treatment of anorexia associated with weight loss in patients with AIDS, as well as nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

4) Confidentiality
   Participating in research may involve a loss of privacy and confidentiality. However, as will be explained below, extensive procedures have been put in place to secure such information.

10. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

    1) Screening
       Subjects will be carefully screened in order to exclude those with any significant medical or psychiatric conditions. The screening process is rigorous, including a SCID, a psychiatric and medical evaluation by a psychiatrist, laboratory tests, ECG, etc., designed to screen out unsuitable subjects.
    2) Phlebotomy
       Due to the risks associated with phlebotomy procedures, subjects who have donated blood within eight weeks of the present study will be excluded. Subjects will be informed that they should not give blood for at least eight weeks prior to the beginning of the study or after completing the trial. Additionally, blood will be drawn by trained nurses or phlebotomists using standard sterile phlebotomy procedures.
    3) Δ^9THC
       The FDA in 1986 granted approval for the use of synthetic Δ^9THC in the treatment of anorexia associated with weight loss in patients with AIDS, as well as nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. Δ^9-THC is also an active ingredient in nabiximols (Sativex patient leaflet), a specific extract of Cannabis, that has been approved in the UK for the alleviation of neuropathic pain, spasticity, overactive bladder,

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

and other symptoms in multiple sclerosis patients. Furthermore, Δ^9-THC has been investigated in a number of clinical trials evaluating its pain reducing effects in various patient populations including multiple sclerosis (23), amyotrophic lateral sclerosis (ALS) (24), fibromyalgia (25), cancer, abdominal hysterectomy (26), headaches (27), spinal cord injury, and muscle spasticity, as well as its symptom reducing effects in obstructive sleep apnea (28), internal pressure in end-stage open-angle glaucoma (29, 30), dementia-related neuropsychiatric symptoms (NPS), progressive inflammatory brain disease, antiemetic effect, colonic motility and sensation. The risks and benefits of Δ^9THC and the specific study procedures will be explained to all participants. After a thorough background of Δ^9THC has been provided, subjects will undergo careful physical, psychiatric and laboratory examinations to assure the clinical appropriateness and safety of their participation in the study. Close clinical monitoring will ensure the appropriateness and safety of subjects' continued participation. As stated previously, the combination of Δ^9THC with PEA may prove to be more safe and effective than Δ^9THC alone.

A subject may withdraw consent and stop the clinical trial at any time. Subjects may be discontinued on the study medication if they develop serious adverse symptoms that are known side effects of dronabinol including cardiac issues (tachycardia >100bpm or hypotension <100/65), physical symptoms (urinary retention, nausea, vomiting, abdominal pain) or psychiatric symptoms (psychotic symptoms or anxiety) that does not resolve with a decrease in dosage of the study medication. The principal investigator of the trial may also withdraw a subject from the trial at any time if he believes the study medication poses a significant health risk to the participant.

4) Confidentiality

All subject information will be kept as confidential as possible. Only members of the investigative research team with appropriate IRB/HIC and HIPPA training will have access to identifying patient information and study data. Data will be maintained and secured in locked file cabinets, on a password protected computer or on an encrypted flash drive, all within a locked room. A numbering coder will be used to assign a unique identifier to each subject. The code number will not be based on any information that could be used to identify subjects (for example, social security number, initials, birth date, etc.) As part of the study procedures, some information about subject participation in this study will become part of their Connecticut Mental Health Center (CMHC) medical record. If a subject does not already have a medical record at CMHC, one will be made for their visit. Furthermore, if a subject has been a patient at YNHH at any time, his or her previous medical records of other visits or admissions will become available to the researchers and to the staff of CMHC when the information collected for this research is added into their medical record. Information will be stored as per HIPPA guidelines. Information will not be dispensed to anyone outside of this research project without prior written authorization from the subject. If it is brought to the attention of the researchers that a child is being abused or neglected, or that there is a risk of harm to the subject or others, this information will be reported to the appropriate authorities. Records will be maintained according to FDA Good Clinical Practice guidelines to ensure protection of confidentiality and security of the records. If requested, participants will be provided

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

with a letter explaining the possibility of a positive drug test for cannabis, to their employer.

11. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study?

       The investigator has assessed the overall risk level for subjects participating in the study to be moderate.

    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?

       N/A

    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://www.yale.edu/hrpp/forms-templates/biomedical.html for
       i. Minimal risk
       ii. Greater than minimal

Moderate Risk DSMP

1. Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency of a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The principal investigator, the IRB and the Human Investigation Committee (HIC) all have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed moderate for the following reasons:
(choose those that apply)

1. We do not view the risks associated with the Dronabinol or PEA as minimal.
2. Given the now established safety and validity of the current use of Dronabinol and PEA, we do not view the proposed studies as high risk.

Although the proposed study has been assessed as one of moderate risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

I. **Attribution of Adverse Events:**

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures/design by the principal investigator (*Michael H. Bloch*) according to the following categories:

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s). b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s). c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s). d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s). e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

II. **Plan for Grading Adverse Events:**

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

III. **Plan for Determining Seriousness of Adverse Events: Serious Adverse Events:**

In addition to grading the adverse event, the principal investigator will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

1. is life-threatening OR
2. results in in-patient hospitalization or prolongation of existing hospitalization OR
3. results in persistent or significant disability or incapacity OR
4. results in a congenital anomaly or birth defect OR
5. results in death OR
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, OR
7. adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

IV. **Plan for reporting Reportable Adverse Events and other unanticipated problems involving risks to subjects or others to the IRB**

The principal investigator will report the following types of events to the IRB: a) adverse events that are serious or life-threatening AND unanticipated (or anticipated but occurring with a greater frequency than expected) AND possibly, probably or definitely related to the drug/device/intervention; and b) other unanticipated problems involving risks to subjects or others.

These adverse events or unanticipated problems involving risks to subjects or others will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website.

V. **Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.**

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

- ✓ All Co-Investigators listed on the protocol
- ✓ Yale Cancer Center Data and Safety Monitoring Committee (DSMC)
- ✓ National Institutes of Health
- ✓ Food and Drug Administration (Physician-Sponsored IND #**131864**)

The principal investigator (*Michael H. Bloch*) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

d. For multi-site studies for which the Yale PI serves as the lead investigator: **N/A**

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?
ii. What provisions are in place for management of interim results?
iii. What will the multi-site process be for protocol modifications?

12. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Go/No-Go Decision for Larger Multi-Site Phase III Trial
The important go/no-go decision is whether the trial, which is not a true efficacy trial but rather a Phase II pilot, provides sufficient encouragement to move forward for a Phase III trial. We propose a series of benchmarks for feasibility, tolerability and preliminary efficacy in an initial trial for go/no-go decision-making. **Feasibility**: Average treatment compliance with the Dronabinol/PEA combination of at least 80% (via pill counts and positive urine drug screen) during the trial. **Tolerability**: Attrition due to AEs of 4 or fewer subjects receiving treatment. **Safety**: Four or fewer subjects have a greater than 20% worsening of tic symptoms while in the trial. **Efficacy:** An average improvement of YGTSS severity of greater than 10% during the course of the 12-week trial.

Assuming all go/no-go decision points are met in the trial, we will additionally use the initial pilot data to design the most appropriate phase III trial design. Specifically, we will examine difference in tic severity as assessed by YGTSS (across all subjects and specifically those assigned to active medication) between week 0 (baseline) and week 12 (endpoint) to determine the time at which treatment benefits likely plateau.

SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. **Identification of Drug, Biologic or Radiotracer:** What is (are) the **name(s)** of the drug(s) biologic(s) or radiotracer(s) being used? Identify whether FDA approval has been granted and for what indication(s).

In addition to PEA, other names of the drug include: Palmitoylethanolamide, C18H37NO2, PeaPure, Normast, Impulsin, MimyX, N-(2-hydroxyethyl)palmitate and N-palmitoylethanolamine. FDA approval has not been granted for the use of PEA. However, PEA is a primary fatty acid amine found in egg yolk. Therefore, it falls under the definition of egg yolk-derived phospholipids, which are listed on the FDA list of "Generally Recognized as Safe" with a designated number GRN No. 411. Content of PEA can also be seen under the FDA List of Indirect Additives Used in Food Contact Substances under general main term: ANIMAL OIL FATTY ACID AMIDES, Doc No. 7625, CAS RN 977139-08-4.

Other names for Δ^9THC include: Δ^9-Tetrahydracannabinol, Dronabinol, Marinol and C21H30O2. Currently, approval has been granted from the FDA for the use of Δ^9THC in the treatment of anorexia associated with weight loss in patients with AIDS, as well as nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

All protocols which utilize a drug, biologic or radiotracer **not** approved by, but regulated by, the FDA, or a radiotracer regulated by the RDRC, must provide the following information:

a. What is the Investigational New Drug (IND) **number** assigned by the FDA? **131864**
b. Who holds the IND? **Michael H. Bloch MD, MS**
c. All protocols which utilize a radiotracer not approved by, but regulated by the FDA must provide the IND number:_____N/A_____
Alternatively, use of the investigational radiotracer may be under RDRC/RSC oversight: (check if appropriate) N/A_____

For all investigational radiotracers, attach a copy of the RDRC/RSC application (for radioisotopes used in the PET Center, PET Center personnel may complete this step)
Go to http://rsc.med.yale.edu/login.asp?url=myApps.asp. When you have logged in, complete the application and attach a copy to this submission.

Alternatively, an **exemption from IND filing requirements** may be sought for a clinical investigation of a drug product that is lawfully marketed in the United States. If there is no IND and an exemption is being sought, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1
The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:

i. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug. ☐ Yes ☐ No
ii. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product. ☐ Yes ☐ No
iii. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. ☐ Yes ☐ No
iv. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56). ☐ Yes ☐ No
v. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs. ☐ Yes ☐ No

Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)

☐ i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):
☐ Blood grouping serum
☐ Reagent red blood cells
☐ Anti-human globulin

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

☐ ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

☐ iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.
   See pages 9-12 under "Background" for this information.

3. **Source:** a) Identify the source of the drug or biologic to be used.
   Therapix Biosciences Ltd.

   b) Is the drug provided free of charge to subjects? ☒ Yes ☐ No
   If yes, by whom?
   Therapix Biosciences Ltd.

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

   Dronabinol will be stored in a well-closed container and in a cool environment between 8° and 15°C (46° and 59°F) such as a refrigerator, as these are the storage recommendations from the FDA. Additionally, arrangements will be made with the CMHC investigational pharmacy regarding proper storage, preparation and stability information for both Dronabinol and PEA.

   Check applicable Investigational Drug Service utilized:

☐ **YNHH IDS**	☐ **Yale Cancer Center**
☒ **CMHC Pharmacy**	☐ **West Haven VA**
☐ **PET Center**	☐ **None**
☐ **Other:**	

Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

5. **Use of Placebo: ☒ Not applicable to this research project**
   If use of a placebo is planned, provide a justification which addresses the following:
   a. Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.
      The following therapies are currently available for the treatment of TS: 1) Neuroleptic medications, 2) atypical neuroleptics, 3) α2-receptors agonists and 4) habit reversal training (HRT).

   b. State the maximum total length of time a participant may receive placebo while on the study.

   c. Address the greatest potential harm that may come to a participant as a result of receiving placebo.

   d. Describe the procedures that are in place to safeguard participants receiving placebo.

6. **Use of Controlled Substances:**
   Will this research project involve the use of controlled substances in human subjects?
   ☒ Yes ☐ No *See HIC Application Instructions to view controlled substance listings*.

   If yes, is the use of the controlled substance considered:
   ☒ Therapeutic: The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.
   ☐ Non-Therapeutic: *Note, the use of a controlled substance in a non-therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License. Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.*

7. **Continuation of Drug Therapy After Study Closure ☐ Not applicable to this project**
   Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?
   ☒ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

   Subjects who report an improvement in the initial 12-week trial will be allowed to continue on the study medication (Dronabinol/PEA combination) free of charge for 6 months as long as they continue to complete clinical assessments every 4 weeks and test positive for cannabis on urine toxicology screen (indicating compliance with study medication). They will be compensated $25 for each follow-up assessment at the conclusion of their participation in the trial.

   ☐ No If no, explain why this is acceptable.

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

B. DEVICES

N/A

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No *If Yes, please be aware of the following requirements*:

a. A YNHH New Product/Trial Request Form must be completed via EPIC: **Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary, " and attach any other pertinent documents. Then select "save and submit" to submit your request**; and

b. Your request must be reviewed and approved **in writing** by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. What is the name of the device to be studied in this protocol?

Has this device been FDA approved? ☐ Yes ☐ No
If yes, state for what indication.

3. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.

4. **Source:**
   a) Identify the source of the device to be used.

   b) Is the device provided free of charge to subjects? ☐ Yes ☐ No

5. What is the PI's assessment of risk level (significant or non-significant) associated with the use of the device?

☐ **Significant Risk (SR) Device Study:** A study of a device that presents a potential for serious risk to the health, safety, or welfare of a participant and 1) is intended as an implant; 2) is used in supporting or sustaining human life; or otherwise prevents impairment of human health; 3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents

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impairment of human health; or 4) otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.

Significant Risk Devices require an Investigational Device Exemption (IDE) issued by the FDA.

What is the **IDE number** assigned by the FDA?

Did the FDA approve this IDE as **Category A** (experimental/investigational) or as **Category B** (non-experimental/investigational)?

Who holds the IDE?

☐ **Non-Significant Risk (NSR) Device Study:** A study of a device that does not meet the definition for a significant risk device and does not present a potential for serious risk to the health, safety, or welfare of participants. Note that if the HIC concurs with this determination, an IDE is not required.

6. **Abbreviated IDE or Exempt IDE:** There are abbreviated requirements for an IDE and there also are exemptions to the requirement for an IDE. *See the criteria in the HIC Application Instructions,* Section VI.B.4 at http://www.yale.edu/hrpp/resources/docs/100FR1aHICProtocol_Application_Instructions5-25-11.pdf *to determine if these pertain to this study.*

☐ **Abbreviated IDE or Exempt IDE** – *If criteria set forth in the HIC Application Instructions are met, copy and paste the completed relevant section from the Instructions into this application.*

7. **Investigational device accountability**:
   a. State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

      Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable):

Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number):

Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations:

Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements:

Distributes the investigational device to subjects enrolled in the IRB-approved protocol:

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:**
   a. targeted for enrollment at Yale for this protocol_18_
   b. If this is a multi-site study, give the total number of subjects targeted across all sites__N/A_

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☒ Flyers	☒ Internet/Web Postings	☐ Radio
☐ Posters	☒ Mass E-mail Solicitation	☒ Telephone
☒ Letter	☒ Departmental/Center Website	☐ Television
☐ Medical Record Review	☒ Departmental/Center Research Boards	☐ Newspaper
☒ Departmental/Center Newsletters	☒ Web-Based Clinical Trial Registries	
☒ YCCI Recruitment database	☒ Clinicaltrials.gov Registry (do not send materials to HIC)	
☐ Other (describe):		

3. **Recruitment Procedures:**
   a. Describe how potential subjects will be identified.

   Subjects will be recruited through the TS/OCD Clinic at the Yale Child Study Center. Additionally, subjects will be contacted through email blast through local TS chapters and by contacting local providers who treat adults with TS. Furthermore, adult subjects that have recently completed other treatment trials for TS at the clinic and agreed to be contacted for future trials will be recruited. Study information, along with the contact phone number, will be posted on clinicaltrials.gov. The YCCI recruitment database and flyers will also be used.

   b. Describe how potential subjects are contacted.

   Research staff will contact adult subjects who have recently completed other treatment trials for TS at the clinic and agreed to be contacted for future studies. All other potential subjects will be asked to contact the research staff through the advertisement methods listed previously.

   c. Who is recruiting potential subjects?

   The clinicians at the Yale TS/OCD (PI and/or co-investigators), as well as the study personnel, members of Dr. Bloch's research team.

4. **Screening Procedures**
   a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☒ Yes ☐ No
   b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION TO BE COLLECTED:
A brief psychiatric and medical history will be collected during telephone screening including Axis I diagnoses, medical and neurologic diagnoses, as well as recent medication and psychotherapy

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

changes. All information will be stored in locked cabinets/password protected computer in an office that is locked. Information that will breach subject confidentiality will not be shared. Rather, data will only be released upon written consent of the subject and will be available for review by the Yale human Investigation Committee. We will hold paper files for seven years at which point they will be destroyed.

HIPAA identifiers:

☒ Names

☒ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

☒ Telephone numbers

☐ Fax numbers

☒ E-mail addresses

☐ Social Security numbers

☐ Medical record numbers

☐ Health plan beneficiary numbers

☐ Account numbers

☒ All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

☐ Certificate/license numbers

☐ Vehicle identifiers and serial numbers, including license plate numbers

☐ Device identifiers and serial numbers

☐ Web Universal Resource Locators (URLs)

☐ Internet Protocol (IP) address numbers

☐ Biometric identifiers, including finger and voice prints

☐ Full face photographic images and any comparable images

☐ Any other unique identifying numbers, characteristics, or codes

5. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects

☒ Yes, some of the subjects

☐ No

If yes, describe the nature of this relationship.

Subjects who have been seen in the clinic may be recruited. Some subjects may be referred for psychopharmacology consult. Other subjects may come specifically because of interest in the study. No subjects will be taken off current medication or withdrawn from ongoing therapy in order to participate in the trial, unless the current medication is ineffective or causes unacceptable adverse effects. Patients who are not interested in the study will be treated in the usual clinical manner.

6. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

Choose one:

☐ For entire study

☒ For recruitment purposes only

☐ For inclusion of non-English speaking subject if short form is being used

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;

A waiver of HIPAA authorized is being requested for recruitment purposes only. Subjects will be initially recruited through word of mouth, TS advocacy organizations, physician referrals and internet ads. PHI such as name, telephone number and email addresses will be needed to schedule initial screening interviews. It would be impractical to coordinate initial subject enrollment and recruitment without this data.

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

Signed authorization is impractical, as the initial screening patients recruited through advertisements or referral may occur via phone or email.

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:
   ☒ Compound Consent and Authorization form
   ☐ HIPAA Research Authorization Form

8. **Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent.

Michael H. Bloch, MD, MS, James F. Leckman, MD, Angeli Landeros-Weisenberger, MD, and Jessica A. Johnson, BS.

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

9. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

Investigators and/or research staff will obtain consent during the initial screening visit. During this visit, all aspects of the study will be discussed and the inclusion criteria will be explained.

10. E**valuation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

The consent documents will be reviewed verbally with the subject. If for any reason, it becomes clear that the subject cannot comprehend trial design or procedures, they will not be enrolled in the study.

11. Documentation of Consent/Assent: Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

Compound Authorization Form

12. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

This protocol will not involve non-English speaking subjects.

12(a) As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?
YES ☐ NO ☐

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are found on our website at: http://www.yale.edu/hrpp/forms-templates/biomedical.html. If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via amendment prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

13. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐ **Not Requesting a consent waiver**
☒ **Requesting a waiver of signed consent**
☐ **Requesting a full waiver of consent**

A. Waiver of **signed** consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6**)

☒ **Requesting a waiver of signed consent for Recruitment/Screening only**

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☒ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☒ Yes ☐ No

OR

c. Does the research activity pose greater than minimal risk?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

☐ **Requesting a waiver of signed consent for the Entire Study (**Note that an information sheet may be required.)

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research pose greater than minimal risk? ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** ☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

B. Full waiver of consent: (No consent from subjects will be obtained for the activity.)

☐ **Requesting a waiver of consent for Recruitment/Screening only**

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

a. Does the research activity pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☐ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

☐ **Requesting a full waiver of consent for the <u>Entire Study</u> (Note: If PHI is collected, information here must match Section VII, question 6.)**

If requesting a full waiver of consent, please address the following:

a. Does the research pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***
☐ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Research staff will collect and use for research the following private identifiable information from subjects after consent is obtained: name, age, address, telephone number, email address, diagnosis, results from the clinical evaluation, clinical rating scales, laboratory tests (blood and urine), electrocardiogram (ECG) and physical examination results. Scientific reports will be written in aggregate terms. Individual responses will not be described if the data is published.

b. How will the research data be collected, recorded and stored?

Clinical data, outcomes of diagnostic instruments and research data will be collected by the principal investigator, co-investigators and study personnel. Collected information will be stored in a locked file cabinet in a locked office. Data will be entered by study personnel into a database, using a secured server, on a password protected computer in a locked office. Data may also be stored on an encrypted flash drive that will be stored in a locked office.

c. How will the digital data be stored? ☐ CD ☐ DVD ☒ Flash Drive ☐ Portable Hard Drive ☒ Secured Server ☒ Laptop Computer ☒ Desktop Computer ☐ Other

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

Do all portable devices contain encryption software? ☒ Yes ☐ No

If no, see http://hipaa.yale.edu/guidance/policy.html

All data will be coded and stored in locked cabinets on a password protected computer, as well as an encrypted flash drive, in a locked office. Private identifiable information about individuals will not be shared. A numbering code will be used to assign a unique identifier to each subject, that of which will be used for data entry stored on all secure electronic devices. Information that will breach subject confidentiality will only be released upon written consent of the subject and will be available for review by the Yale Human Investigation Committee. A Certificate of Confidentiality *has been* obtained.

e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

Paper files will be held for seven years after the completion of the study. After that point, all paper files will be destroyed. As noted previously, archived computer files will not have any identifying patient information.

f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

The principal investigator, co-investigators and all study personnel.

g. If appropriate, has a Certificate of Confidentiality been obtained?

h. *YES* Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.

Yes. Evidence of abuse or situations in which the subject is deemed a danger to self or others will be reported.

SECTION IX: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

Subjects may benefit from the medical and psychiatric evaluations that they will receive while participating in the study. Patients will receive a higher level of evaluation and care than routine treatment.

APPROVED BY THE YALE UNIVERSITY IRB 9/27/2017 VALID THROUGH 10/25/2018

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

   Subjects may continue any current mediations or therapy, those of which might include various antipsychotics or alpha-2 antagonists, as well as habit reversal therapy. All of these interventions have demonstrated efficacy for the treatment of TS. Subjects will be presented with the risks and benefits of each of the treatments. Additionally, subjects will be offered any of the previously stated treatments that they have not received prior to enrolling in the trial.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   Participants may be paid up to $650 total as compensation for participating in this study. They will receive a stipend payment of $80 for the in-person screening assessment, $70 for the Baseline, Week 4, Week 8, and Week 12 assessments; and $35 for the Week 1, Week 2, Week 6 and Week 10 assessments. Additionally, They will receive a stipend payment of $25 for each clinical follow-up assessment that you complete. Follow-up assessments will take place every 4 weeks for 6 months, after the end of the initial 12-week trial. Participants will receive such payments only for those visits that are completed.

   If the participant travels more than 50 miles each way in order to participate in the study, they also may receive reimbursement for reasonable lodging and travel expenses in addition to the stipend outlined above, up to a total of $200.00 per visit. Participants will need to provide receipts of your costs to the study coordinator.

   According to the rules of the Internal Revenue Service (IRS), payments that are made to research subjects as a result of their participation in a study may be considered taxable income.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   Subjects will not be charged for the study medications, clinical assessments, services or laboratory tests directly related to the study. As previously noted, some subjects may be seen for a clinical consultation at the Yale Child Study Center TS/OCD Clinic piror to study entry. Clinical consultation will be charged as part of care in the usual manner.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
   a. Will medical treatment be available if research-related injury occurs?
      Yes

   b. Where and from whom may treatment be obtained?

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Initial assessment and appropriate referral will be carried out by the research team. The PI (Michael H. Bloch, MD, MS) will conduct an assessment to determine whether the events were considered "related to the study treatment" or not. The research team will participate in assessment and appropriate disposition of the case. Disposition has taken many forms: assumed ongoing clinical care of the subject, securing of appropriate referrals and discontinued involvement in the patient's care, as well as a combined approach in which care is provided in collaboration with appropriate specialists. In all cases, the disposition is guided by the family's preference and clinical judgment regarding the subject's best interest. Every reasonable effort will be made to incorporate the interest of the subject's primary care provider.

c. Are there any limits to the treatment being provided?

The intervention will focus on assessment and securing an appropriate referral in collaboration with the family and the primary care provider.

d. Who will pay for this treatment?

Assessment and referral services will be provided without charge. Ongoing care will be paid for by the family or the family's insurance carrier.

e. How will the medical treatment be accessed by subjects?

As previously noted, the occurrence of an adverse event requiring care outside of the confines of the study will initially be assessed by the research time. Referral's to the family's primary care provider or other specialists will be made in accordance with the nature of the subject's problem.

Note In order to simply and clarify these points in the consent form, the following statement was added to the compound authorization form:

"If you are injured during your participation in this study, treatment will be provided, but you or your insurance company will be responsible for the cost of this treatment. There are no provisions for financial compensation for injuries. You do not give up any of your legal rights by signing this form."

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APPENDIXES:

Appendix 1: Previous Trials of Δ^9-tetrahydracannabinol

Primary Medical Condition	Number of Patients	Administered Drug	Main Results	Reference
Central neuropathic pain in patients with multiple sclerosis	24 patients aged between 23 and 55 years	Orally administered dronabinol at a maximum dose of 10 mg daily or corresponding placebo f or three weeks (15-21 days), separated by a three week washout period.	Median spontaneous pain intensity was significantly lower during dronabinol treatment than during placebotreatment (4.0 (25th to 75th centiles 2.3 to 6.0) v 5.0 (4.0 to 6.4), P = 0.02), and median pain relief score (numerical rating scale) was higher (3.0 (0 to 6.7) v> 0 (0 to 2.3), P = 0.035). The functional ability of the multiple sclerosis patients did not change.	Svendsen, K. B., Jensen, T. S., and Bach, F. W. (2004). Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ. 329: 253-260
Central neuropathic pain in patients with multiple sclerosis	339 patients	Sativex	Interim analysis at week 10 showed a statistically significant treatment difference in favor of THC/CBD spray at this time point (p = 0.046). During the randomized-withdrawal phase, the primary endpoint of time to treatment failure was statistically significant in favor of THC/CBD spray, with 57 % of patients receiving placebo failing treatment versus 24 % of patients from the THC/CBD spray group (p = 0.04).	Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol. 2013;260 (4):984-997

Central neuropathic pain in patients with multiple sclerosis		Cannabis based medicinal extracts (CBME)		Young CA, Rog DJ. (2003) Randomised controlled trial of cannabis based medicinal extracts (CBME) in central neuropathic pain due to multiple sclerosis. Paper presented at: IV Congress of the European Federation of IASP Chapters (EFIC); September 2-6, 2003; Prague, Czech Republic.
Multiple sclerosis-induced neuropathic pain	15 relapsing-remitting MS patients with MS-induced NPP	Nabilone or placebo was titrated over 4 weeks (0.5 mg/week increase) followed by 5-week maintenance of 1 mg oral nabilone (placebo) twice daily in patients stabilized on GBP	Significant group × time(2) interaction term was reported for both the VAS pain ($P < 0.01$) and VASimpact score ($P < 0.01$), demonstrating the adjusted rate of decrease for both outcomes was statistically greater in nabilone vs placebo study group.	Turcotte D, Doupe M, Torabi M, Gomori A, Ethans K, Esfahani F, Galloway K, Namaka M (2015) Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. Pain Med. 2015 Jan;16(1):149-59

Central pain in multiple sclerosis (MS)	66 patients with MS and central pain states (59 dysesthetic, seven painful spasms)	Whole-plant cannabis-based medicine (CBM), containing delta-9-tetrahydrocannabinol:cannabidiol (THC:CBD) delivered via an oromucosal spray, as adjunctive analgesic treatment (Each spray delivered 2.7 mg of THC and 2.5 of CBD, and patients could gradually self-titrate to a maximum of 48 sprays in 24 hours.)	CBM was superior to placebo in reducing the mean intensity of pain (CBM mean change -2.7, 95% CI: -3.4 to -2.0, placebo -1.4 95% CI: -2.0 to -0.8, comparison between groups, p = 0.005) and sleep disturbance (CBM mean change -2.5, 95% CI: -3.4 to -1.7, placebo -0.8, 95% CI: -1.5 to -0.1, comparison between groups, p = 0.003).	Rog, D. J., Nurmikko, T. J., Friede, T., and Young, C. A. (2005). Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 65: 812-819.
Central pain in multiple sclerosis (MS)	24 MS patients	Dronabinol	Dronabinol reduced the spontaneous pain intensity significantly compared with placebo (4.0 (2.3-6.0) vs. 5.0 (4.0-6.4), median (25th-75th percentiles), p = 0.02).	Svendsen KB, Jensen TS, Bach FW. (2005) [Effect of the synthetic cannabinoid dronabinol on central pain in patients with multiple sclerosis–secondary publication]. Ugeskr Laeger. 167(25-31):2772-2774

Central neuropathic pain from brachial plexus avulsion	48 patients	THC 25 mg/ml or THC:CBD 25 mg/ml given as patient activated oromucosal 100ul sprays or placebo	Pain VAS was 6.1 for THC and THC:CBD compared to 6.7 for placebo, 11-point box scale was 43.6 for THC and 45.1 for THC:CBD, compared to 52.9 for placebo.	Berman J, Lee J, Cooper M, et al. (2003) Efficacy of two cannabis-based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Paper presented at: Pain Society Annual Meeting; April 1-4, 2003; Glasgow, United Kingdom. Anaesthesia. 2003;58(9):938
Chronic pain associated with brachial plexus root avulsion	48 patients with at least one avulsed root and baseline pain score of four or more on an 11-point ordinate scale	Placebo and two whole plant extracts of Cannabis sativa L.: GW-1000-02 (Sativex), containing Delta(9)tetrahydrocannabinol (THC):cannabidiol (CBD) in an approximate 1:1 ratio and GW-2000-02, containing primarily THC	The primary outcome measure (mean pain severity score during the last 7 days of treatment) failed to fall by the two points defined in our hypothesis. However, both this measure and measures of sleep showed statistically significant improvements. The study medications were generally well tolerated with the majority of adverse events, including intoxication type reactions, being mild to moderate in severity and resolving spontaneously.	Berman, J. S., Symonds, C., and Birch, R. (2004). Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain. 112: 299-306.

Neuropathic pain		Mild dose cannabis 3.53% THC by weight, Low dose cannabis 1.29% THC by weight, Placebo cannabis placebo marijuana.	The primary outcome variable, VAS Pain Intensity, was assessed by asking participants to indicate the intensity of their current pain on a 100-mm visual analog scale (VAS) between 0 (no pain) and 100 (worst possible pain).An assessment was performed before the administration of vaporized cannabis or placebo and hourly thereafter for six hours.	University of California Davis. Center for Medicinal Cannabis Research, VA Northern California Health Care System. Effects of vaporized marijuana on neuropathic pain. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT01037088. Accessed April 7, 2014
Neuropathic pain		High dose cannabis (7.5% THC by weight), Low dose cannabis (3.5% THC by weight), and Placebo cannabis	Score on a series of pain scales (heat pain threshold, VAS intensity, VAS unpleasantness, pain relief, neuropathic pain scale) was assessed	Center for Medicinal Cannabis Research. Effects of smoked marijuana on neuropathic pain. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00254761. Accessed April 7, 2014
Neuropathic pain	38 patients with central and peripheral neuropathic pain	High-dose (7%), low-dose (3.5%), or placebo cannabis	A mixed linear model demonstrated an analgesic response to smoking cannabis. No effect on evoked pain was seen. Psychoactive effects were minimal and well-tolerated, with some acute cognitive effects, particularly with memory, at higher doses.	Wilsey, B., Marcotte, T., Tsodikov, A., Millman, J. and others. (2008). A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J.Pain. 9: 506-521

Pain of neurological origin	70	GW-1000-02 vs placebo	Change From Baseline in Mean Pain Box Scale-11 Score at 3 Weeks was -1.3 (1.67) for GW-1000-02 and -0.9 (1.62) for placebo, while Use of Analgesic Escape Medication was 20.57 (33.08) for GW-1000-02, comparing to 50.12 (44.10) for placebo	GWPharmaceuticals Ltd. A study to evaluate the effects of cannabis based medicine in patients with pain of neurological origin. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT01606176 Accessed April 7, 2014
Chronic pain	1 56-year-old man who developed chronic pain following the excision of a facial cancer	Nabilone	Condition was poorly controlled despite multiple analgesic medications. Following the starting of nabilone (a synthetic cannabinoid) his pain control was greatly improved and this had a huge impact on his quality of life.	Reynolds TD, Osborn HL (2013) The use of cannabinoids in chronic pain. BMJ Case Rep. 2013 Jul 26;
Chronic pain	30 patients taking opioids for chronic pain	Dronabinol (Marinol capsules; Solvay Pharmaceuticals, Brussels, Belgium) 10 mg or 20 mg	Patients who received dronabinol experienced decreased pain intensity and increased satisfaction compared with placebo. No differences in benefit were found between the 20 mg and 10 mg doses.	Narang, S., Gibson, D., Wasan, A. D., Ross, E. L. and others. (2008). Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. J.Pain. 9: 254-264

Chronic pain	30 patients	Nabilone (1/4)-1 mg/day)	Throughout the cross-over periods the nabilone treatment was superior (medians [25%-; 75%-percentiles]: nabilone/placebo): decrease of the average spinal pain intensity within the last 4 weeks (DeltaVAS) 0.9 [0.0; 2.0] / 0.5 [0.0; 1.7], decrease of the current spinal pain intensity (DeltaVAS) 0.6 [0.0; 2.5] / 0.0 [-1.0, 1.0] (p = .006), decrease of the average headache intensity within the last 4 weeks (DeltaVAS) 1.0 [-1.0; 2.4] / 0.2 [-0.9; 1.0], increase of the number of days without headache within the last 4 weeks 2.0 [0.0; 6.5] / 0.0 [-5.0; 4.0], increase of the quality of life (DeltaQOL-Score) 5.0 [0.8; 10.8] / 2.0 [-2.3; 8.0].	Pinsger M, SchimettaW, Volc D, Hiermann E, Riederer F, PolzW. (2006) [Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain—a randomized controlled trial]. Wien KlinWochenschr. 118(11-12):327-335
Chronic pain	30	Dronabinol (Marinol) as Add-On Therapy for Patients on Opioids		Brigham andWomen's Hospital; Solvay Pharmaceuticals. Study to evaluate the efficacy of dronabinol (Marinol) as add on therapy for patients on opioids for chronic pain. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00153192. Accessed April 7, 2014

Chronic back pain		(synthetic cannabinomimeticum)		Pinsger M. (2012) Benefit of an add-on-treatment with a synthetic cannabinomimeticum on patients with chronic back pain-a randomized controlled trial. Paper presented at 8th International Conference on Early Psychosis: From Neurobiology to Public Policy; October 11-13, 2012; San Francisco: CA. Eur Spine J. 21(11):2366
Chronic Central Neuropathic Pain and Fibromyalgia	124	7.5 mg delta 9-THC over 7 months	Psychometric parameters (PDI, SF-12, QLIP, HADS) and pain intensity improved significantly during delta 9-THC treatment. Opioid doses were reduced and patients perceived THC therapy as effective with tolerable side effects. About 25% of the patients, however, did not tolerate the treatment.	Weber, J., Schley, M., Casutt, M., Gerber, H. and others. (2009). Tetrahydrocannabinol (Delta 9-THC) Treatment in Chronic Central Neuropathic Pain and Fibromyalgia Patients: Results of a Multicenter Survey. Anesthesiol.Res.Pract. 2009: 827290.-
Chronic neuropathic pain	100	Nabilone and dihydrocodeine	Mean pain score as measured by VAS 0 - 10 for the last two weeks on treatment	Cambridge Laboratories Ltd. A randomised, crossover, double blind comparison of the analgesic effect and patient tolerability of Nabilone and dihydrocodeine in chronic neuropathic pain. metaRegister of Controlled Trials. http://isrctn.org/ISRCTN15330757. Accessed April 7, 2014

Chronic neuropathic pain	21 patients	Ajulemic acid (AJA) or placebo capsules	The results showed no significant reduction in mechanical hypersensitivity (p=0.052), although a tendency towards pain reduction could be seen. The VAS score showed significant pain reduction (p=0.021) and NNT values for 30% pain relief were 2.14 for the first treatment group and 5.29 for the second treatment group. No significant findings were observed regarding psychotropic or physical measurements.	Salim K, Schneider U, Burstein S, Hoy L, Karst M. (2005) Pain measurements and side effect profile of the novel cannabinoid ajulemic acid. Neuropharmacology 48(8):1164-71
Chronic neuropathic pain	21 patients (8 women and 13 men) aged 29 to 65 years (mean, 51 years)	1',1'dimethylheptyl-Delta8-tetrahydrocannabinol-11-oic acid (CT-3), a potent analog of THC-11-oic acid (Two daily doses of CT-3 (four 10-mg capsules per day) or identical placebo capsules)	The mean differences over time for the VAS values in the CT-3-placebo sequence measured 3 hours after intake of study drug differed significantly from those in the placebo-CT-3 sequence (mean [SD], -11.54 [14.16] vs 9.86 [21.43]; P =.02).	Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. (2003) Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. JAMA. 290(13): 1757-1762

Chronic neuropathic pain	96 patients with chronic neuropathic pain, aged 23-84 years	Maximum daily dose of 240 mg dihydrocodeine or 2 mg nabilone	The mean score was 6.0 mm longer for nabilone than for dihydrocodeine (95% confidence interval 1.4 to 10.5) in the available case analysis and 5.6 mm (10.3 to 0.8) in the per protocol analysis. Dihydrocodeine provided better pain relief than nabilone and had slightly fewer side effects.	Frank B, Serpell MG, Hughes J, Matthews JNS, Kapur D. (2008) Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. BMJ. 336 (7637):199-201
Chronic neuropathic pain		Cannabis containing 9.43% THC versus cannabis containing 0% THC		Montreal General Hospital. Pilot study of smoked cannabis for chronic neuropathic pain. metaRegister of Controlled Trials (mRCT), http://www.controlledtrials.com/ISRCTN68314063 Accessed April 7, 2014.
Central neuropathic pain		Sativex		Berman J, Bosworth T, Guy G, Stott C; Sativex Spinal Cord Injury Study Group. Sativex in the treatment of central neuropathic pain due to spinal cord injury: a randomised controlled study. Paper presented at: British Pain Society Annual Scientific Meeting; April 2007; Glasgow: United Kingdom.

Central neuropathic pain	339	Sativex vs placebo	Change From Baseline in Mean Pain Due to MS NRS Score was -2.02 (2.15) for Sativex and -1.89 (2.33) for placebo, while Change in Pain From Baseline to End of the Treatment Using the NPS (Neuropathic Pain Scale) was -14.24 (18.17) for Sativex, comparing to -11.44 (17.86) for placebo.	GWPharmaceuticals Ltd. Sativex versus placebo when added to existing treatment for central neuropathic pain inMS. http://ClinicalTrials.gov/show/NCT00391079 Accessed April 7, 2014
Neuropathic pain despite traditional treatment	39 patients with central and peripheral neuropathic pain	Inhaling medium-dose (3.53%), low-dose(1.29%), or placebo cannabis	There was no significant difference between the 2 active dose groups' results (P > .7). The number needed to treat (NNT) to achieve 30% pain reduction was 3.2 for placebo versus low-dose, 2.9 for placebo versus medium-dose, and 25 for medium- versus low-dose. As these NNTs are comparable to those of traditional neuropathic painmedications, cannabis has analgesic efficacy with the low dose being as effective a pain reliever as the medium dose. Psychoactive effects were minimal and well tolerated, and neuropsychological effects were of limited duration and readily reversible within 1 to 2 hours.	Wilsey, B., Marcotte, T., Deutsch, R., Gouaux, B. and others. (2012). Low-Dose Vaporized Cannabis Significantly Improves Neuropathic Pain. J.Pain. 14: 136-148

Peripheral Neuropathic Pain, characterized by Allodynia	80	THC CBD, 1:1 and placebo	GWPharma Ltd. A double blind, randomised, placebo controlled parallel group study of cannabis based medicine extract (CBME), in the treatment of peripheral neuropathic pain characterised by allodynia. metaRegister of Controlled Trials. http://www.controlled-trials.com/ISRCTN38250575 Accessed April 7, 2014
Peripheral Neuropathic Pain, characterized by Allodynia		Sativex Ongoing	GWPharma Ltd. A double blind, randomised, placebo controlled, parallel group study of Sativex, in the treatment of subjects with peripheral neuropathic pain associated with allodynia. EU Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctrsearch/search?query=eudract_number:2004-002531-32. Accessed April 8, 2014.

Neuropathic pain characterized by allodynia		Sativex		Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ. (2005) A multi-centre, double-blind, randomized, controlled trial of oro-mucosal cannabis based medicine in the treatment of neuropathic pain characterized by allodynia. Neurology. 64(suppl 1):A374
Pain and allodynia	125	Oro-mucosal sativex, (THC: CBD)	The mean reduction in pain intensity scores (primary outcome measure) was greater in patients receiving sativex than placebo (mean adjusted scores -1.48 points vs. -0.52 points on a 0-10 Numerical Rating Scale ($p=0.004$; 95% CI: -1.59, -0.32). Improvements in Neuropathic Pain Scale composite score ($p=0.007$), sleep NRS ($p=0.001$), dynamic allodynia ($p=0.042$), punctate allodynia ($p=0.021$), Pain Disability Index ($p=0.003$) and Patient's Global Impression of Change ($p<0.001$) were similarly greater on sativex vs. placebo. Sedative and gastrointestinal side effects were reported more commonly by patients on active medication.	Nurmikko, T. J., Serpell, M. G., Hoggart, B., Toomey, P. J. and others. (2007). Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain. 133: 210-220

Pain due to rheumatoid arthritis(RA)	58 patients over 5 weeks	CBM (Sativex) and placebo	In comparison with placebo, the CBM produced statistically significant improvements in pain on movement,pain at rest, quality of sleep, DAS28 and the SF-MPQ pain at present component. There was no effect on morning stiffness but baseline scores were low. The large majority of adverse effects were mild or moderate.	Blake, D. R., Robson, P., Ho, M., Jubb, R. W. and others. (2006). Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology. (Oxford). 45: 50-52.
TMJ pain caused by osteoarthritis	24	300mg at morning + 600mg at evening for 7 days; followed by 300mg/bid for 7 days Vs ibupfofen (600 mg/tid for 14 days)	Among the completers, pain relief was greater with cannabis than placebo (median difference in DDS pain intensity change, 3.3 points, effect size=0.60; p=0.016). The proportions of subjects achieving at least 30% pain relief with cannabis versus placebo were 0.46 (95%CI 0.28, 0.65) and 0.18 (0.03, 0.32).	Ellis, R. J., Toperoff, W., Vaida, F., van den Brande, G. and others. (2009). Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology. 34: 672-680
Analgesia		Delta(9)-THC 5 mg orally or placebo and 90 min later morphine 0.02 mg/kg intravenously or placebo	Among affective responses, although neither morphine nor Delta(9)-THC had a significant effect, there was a positiveanalgesic interaction between the two (p = 0.012), indicating that the combination had a synergistic affective analgesic effect.	Roberts, J. D., Gennings, C., and Shih, M. (2006). Synergistic affective analgesic interaction between delta-9-tetrahydrocannabinol and morphine. Eur.J.Pharmacol. 530: 54-58.

Noncancer pain	30 chronic noncancer pain patients taking opioids and not using marijuana	Placebo, 10 or 20 mg dronabinol	The 10 and 20 mg dronabinol doses had significantly elevated scores over time on 4/5 subscales versus placebo (P<0.05). Average daily morphine use, total pain relief (TOTPAR), age, sex, and baseline pain level were not significant covariates. ARCI peak effects at 2 hours were similar to peak effects of smoked marijuana at 30 minutes (P=0.80, 10 mg=low strength, 20 mg=high strength).	Issa MA, Narang S, Jamison RN, Michna E, Edwards RR, Penetar DM, Wasan AD (2014) The subjective psychoactive effects of oral dronabinol studied in a randomized, controlled crossover clinical trial for pain. Clin J Pain. 30(6):472-8
Chronic noncancer pain	20	Nabilone followed up for an average of 1.5 years	Fifteen patients reported subjective overall improvement with nabilone, and nine reported reduced pain intensity. Beneficial effects on sleep and nausea were the main reasons for continuing use. Intolerable side effects were experienced in three patients (palpitations, urinary retention, dry mouth).	Berlach, D. M., Shir, Y., and Ware, M. A. (2006). Experience with the synthetic cannabinoid nabilone in chronic noncancer pain. Pain Med. 7: 25-29
Post-traumatic or postsurgical neuropathic pain	23, 2 weeks	Cannabis at four potencies (0%, 2.5%, 6% and 9.4% tetrahydrocannabinol)	A single inhalation of 25 mg of 9.4% tetrahydrocannabinol herbal cannabis three times daily for five days reduced the intensity of pain, improved sleep and was well tolerated.	Ware, M. A., Wang, T., Shapiro, S., Robinson, A. and others. (2010). Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ. 182: E694-E701

Pain tolerance		Marijuana and placebo	A statistically significant increase in tolerance was observed after smoking marijuana. Although there was no statistically significant interaction between the drug effect and having had previous cannabis experience, there was a definite trend towards a greater increase for the experienced (16%) compared to the naive group(8%).	Milstein, S. L., MacCannell, K., Karr, G., and Clark, S. (1975). Marijuana-produced changes in pain tolerance. Experienced and non-experienced subjects. Int.Pharmacopsychiatry. 10: 177-182
Antinociception	5 male regular marijuana users	Marijuana (3. 55% Delta(9)-tetrahydrocannabinol (Delta(9)-THC) (active))	Marijuana produced significant dose-dependent antinociception (increased finger withdrawal latency) and biobehavioral effects. Naltrexone did not significantly influence marijuana dose-effect curves, suggesting no role of endogenous opiates in marijuana-induced antinociception under these conditions.	Greenwald, M. K. and Stitzer, M. L. (2000). Antinociceptive, subjective and behavioral effects of smoked marijuana in humans. Drug Alcohol Depend. 59: 261-275

Pain and hyperalgesia induced by intradermal capsaicin	15 healthy volunteers	Low-, medium-, and high-dose smoked cannabis (respectively 2%, 4%, and 8% 9-delta-tetrahydrocannabinol by weight)	By 45 min aftercannabis exposure, there was a significant decrease in capsaicin-induced pain with the medium dose and a significant increase in capsaicin-induced pain with the high dose. There was no effect seen with the low dose, nor was there an effect on the area of hyperalgesia at any dose. Significant negative correlations between pain perception and plasma delta-9-tetrahydrocannabinol levels were found after adjusting for the overall dose effects. There was no significant difference in performance on the neuropsychological tests.	Wallace, M., Schulteis, G., Atkinson, J. H., Wolfson, T. and others. (2007). Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. Anesthesiology. 107: 785-796
Capsaicin-induced pain and hyperalgesia	30 healthy male volunteers	Single doses of nabilone (1, 2 or 3 mg)	Pain and hyperalgesia were measured at baseline and 2-3.5 h after dosing. Nabilone did not significantly attenuate either ongoing pain or primary or secondary hyperalgesia, whereas dose-dependent CNS effects were observed from 1.5 to 6 h after dosing, being maximal at 4-6 h.	Kalliomaki, J., Philipp, A., Baxendale, J., Annas, P. and others. (2012). Lack of effect of central nervous system-active doses of nabilone on capsaicin-induced pain and hyperalgesia. Clin.Exp.Pharmacol.Physiol. 39: 336-342
Anti-hyperalgesic properties upon capsaicin stimulation		Cannabinoid receptor ligand HU210	Pre-treatment with HU210 significantly reduced the perception of pain following the administration of capsaicin.	Rukwied, R., Watkinson, A., McGlone, F., and Dvorak, M. (2003). Cannabinoid agonists attenuate capsaicin-induced responses in human skin. Pain. 102: 283-288

Pain	12 healthy volunteers	THC (20 mg), morphine (30 mg), THC-morphine (20 mg THC+30 mg morphine), or placebo were given orally and as single doses	THC did not significantly reduce pain. In the cold and heat tests it even produced hyperalgesia, which was completely neutralized by THC-morphine. A slight additive analgesic effect could be observed for THC-morphine in the electrical stimulation test. No analgesic effect resulted in the pressure and heat test, neither with THC nor THC-morphine. Psychotropic and somatic side-effects (sleepiness, euphoria, anxiety, confusion, nausea, dizziness, etc.) were common, but usually mild.	Naef, M., Curatolo, M., Petersen-Felix, S., Arendt-Nielsen, L. and others. (2003). The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. Pain. 105: 79-88
Pain due to spinal cord injury (SCI)	116	GW-1000-02 (THC (27 mg/ml) and CBD (25 mg/ml) delivered in 100 microlitre actuations by a pump action oromucosal spray) vs placebo	Change From Baseline in Mean Central Neuropathic Pain at the End of Treatment (up to 51 Days) was -0.74 (1.12) for GW-1000-02 and -0.69 (1.39) for placebo, while change From Baseline in the Mean Percentage of Days on Which Escape Medication Was Used at the End of Treatment was -4.68 (18.25) and -2.91 (20.83) respectively.	GWPharmaceuticals Ltd. A study of cannabis based medicine extracts and placebo in patients with pain due to spinal cord injury. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT01606202. Accessed April 7, 2014

Diabetic painful peripheral neuropathy	17	Inhaled cannabis (400mg placebo or active cannabis administered via the Volcano vaporizer)		Center for Medicinal Cannabis Research. Efficacy of inhaled cannabis in diabetic painful peripheral neuropathy. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00781001. Accessed April 7, 2014
Diabetic painful peripheral neuropathy		Sativex	ongoing	GWPharma Ltd. A double blind, randomised, placebo controlled, parallel group study of Sativex in the treatment of subjects with pain due to diabetic neuropathy. EU Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctrsearch/search?query=eudract_number:2004-002530-20. Accessed August 4, 2014
Peripheral neuropathic pain (PNP)	380 patients with PNP associated with diabetes or allodynia	Delta-9-tetrahydrocannabinol(THC)/cannabidiol (CBD) oromucosal spray	The pain NRS showed a decrease in score over time in patients from a mean of 6.9 points (baseline in the parent studies) to a mean of 4.2 points (end of open-label follow-up) (38-week).	Hoggart B, Ratcliffe S, Ehler E, Simpson KH, Hovorka J, Lejčko J, Taylor L, Lauder H, Serpell M. (2015) A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain. J Neurol. Jan; 262(1):27-40

Peripheral neuropathic pain (PNP)	303 patients with PNP associated with allodynia	THC/CBD spray vs placebo	At the 30% responder level, there were statistically significant treatment differences in favour of THC/CBD spray in the full analysis (intention-to-treat) dataset [p = 0.034; 95% confidence interval (CI): 1.05-3.70]. There was also a reduction in mean PNP 0-10 NRS scores in both treatment groups that was numerically higher in the THC/CBD spray group, but which failed to reach statistical significance.	Serpell M, Ratcliffe S, Hovorka J, et al. (2014) A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain. 18(7):999-1012
Painful diabetic peripheral neuropathy	16 patients with painful diabetic peripheral neuropathy	Placebo or low (1% tetrahydrocannabinol [THC]), medium (4% THC), or high (7% THC) doses of cannabis (Aerosolized cannabis or placebo)	Dose-dependent reduction in diabetic peripheral neuropathy pain in patients with treatment-refractory pain.	Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH (2015) Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy. J Pain. 16(7):616-27

Painful diabetic peripheral neuropathy	30 subjects with intractable PDN unresponsive to currently available treatments	Sativex or placebo	There was a substantial and significant improvement in pain scores in both groups over the course of the study. There was, however, no significant difference between the two treatment arms for the primary outcome measures.	Selvarajah D, Gandhi RA,Witte D, Bowler H, Emery C, Tesfaye S. (2006) Treatment of painful diabetic neuropathy with Sativex (a cannabis based medicinal product)—results of a randomized placebo controlled trial. Diabetologia. 2006;49 (suppl 1):671-672
Diabetic painful peripheral neuropathy		Sativex	The mean daily pain due to diabetic neuropathy on a 0-10 NRS score during the last seven days of treatment was assessed	GWPharmaceuticals Ltd. A study of sativex® for pain relief due to diabetic neuropathy. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00710424. Accessed April 7, 2014
Refractory human diabetic peripheral neuropathic pain (DPN)	26	Nabilone, 9 weeks	Improvement in the change in mean end-point neuropathic pain vs placebo (mean treatment reduction of 1.27; 95% confidence interval 2.29-0.25, P=0.02), with an average nabilone dose at end point of 2.9 ± 1.1mg/day, and improvements from baseline for the anxiety subscale of the Hospital Anxiety and Depression Scale, the Medical Outcomes Study sleep scale problems index, and the European Quality of Life-5-Domains index score (each P<0.05).	Toth, C., Mawani, S., Brady, S., Chan, C. and others. (2012). An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain. 153: 2073-2082

Adjuvant treatment in painful diabeticperipheral neuropathy (DPN).	30	Sativex or placebo	Significant improvement in pain scores in both groups, but mean change between groups was not significant.	Selvarajah, D., Gandhi, R., Emery, C. J., and Tesfaye, S. (2010). Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care. 33: 128-130
HIV-related painful peripheral neuropathy		Smoked cannabis		Abrams DI, Jay CA, Vizoso H, et al. Smoked cannabis therapy for HIV-related painful peripheral neuropathy: results of a randomized, placebo-controlled clinical trial. Paper presented at: IACM 3rd Conference on Cannabinoids in Medicine; September 9-10, 2005; Leiden, the Netherlands.
HIV-related painful peripheral neuropathy		Smoked cannabis: Active cannabis (1-8% THC by weight) vs Placebo cannabis		Center for Medicinal Cannabis Research. Medicinal cannabis for painful HIV neuropathy. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00255580. Accessed April 7, 2014.

Neuropathic pain of HIV-associated sensory neuropathy	50	Cannabis (3.56% tetrahydrocannabinol) or identical placebo cigarettes	Smoked cannabis reduced daily pain by 34% (median reduction; IQR = -71, -16) vs 17% (IQR = -29, 8) with placebo (p = 0.03). Greater than 30% reduction in pain was reported by 52% in thecannabis group and by 24% in the placebo group (p = 0.04).	Abrams, D. I., Jay, C. A., Shade, S. B., Vizoso, H. and others. (2007). Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 68: 515-521
HIV derived pain and other medical symptoms	HIV-positive individuals attending a large clinic (523)	Cannabis	Patients reported improved appetite (97%), muscle pain (94%), nausea (93%), anxiety (93%), nerve pain (90%), depression (86%), and paresthesia (85%). Many cannabis users (47%) reported associated memory deterioration.	Woolridge, E., Barton, S., Samuel, J., Osorio, J. and others. (2005). Cannabis use in HIV for pain and other medical symptoms. J.Pain Symptom.Manage. 29: 358-367.
Pain management and quality of life improvement in patients with fibromyalgia	40	Nabilone, from 0.5 mg PO at bedtime to 1 mg BID over 4 weeks	Significant decreases in the VAS (-2.04, P < .02), FIQ (-12.07, P < .02), and anxiety (-1.67, P < .02) in the nabilone treated group at 4 weeks.	Skrabek, R. Q., Galimova, L., Ethans, K., and Perry, D. (2008). Nabilone for the treatment of pain in fibromyalgia. J.Pain. 9: 164-173

Pain and other symptoms in patients with IBD	100 patients with ulcerative colitis (UC) and 191 patients with Crohn's disease (CD) attending a tertiary-care outpatient clinic completed a questionnaire	Cannabis	Patients were more likely to usecannabis for symptom relief if they had a history of abdominal surgery [29/48 (60%) vs. 24/74 (32%); P=0.002], chronic analgesic use [29/41 (71%) vs. 25/81 (31%); P<0.001], complimentary alternative medicine use [36/66 (55%) vs. 18/56 (32%); P=0.01] and a lower short inflammatory bowel disease questionnaire score (45.1±2.1 vs. 50.3±1.5; P=0.03).	Lal, S., Prasad, N., Ryan, M., Tangri, S. and others. (2011). Cannabis use amongst patients with inflammatory bowel disease. Eur.J.Gastroenterol.Hepatol. 23: 891-896
Acute inflammatory pain and hyperalgesia	18 healthy female volunteers	Capsules containing Delta-tetrahydrocannabinol-standardized cannabis extract or active placebo (orally)	Cannabis extract did not affect heat pain thresholds in the sunburn model. Electrical thresholds (250 Hz) were significantly lower compared with baseline and placebo. In the capsaicin model, the area of secondary hyperalgesia, flare, and spontaneous pain were not altered.	Kraft, B., Frickey, N. A., Kaufmann, R. M., Reif, M. and others. (2008). Lack of analgesia by oral standardized cannabis extract on acute inflammatory pain and hyperalgesia in volunteers. Anesthesiology. 109: 101-110

Chronic pain in patients with advanced cancer	43 patients with cancer-related pain experiencing inadequate analgesia despite chronic opioid dosing	Patients self-titrated THC/CBD spray (n=39) or THC spray (n=4)	Long-term use of THC/CBD spray was generally well tolerated, with no evidence of a loss of effect for the relief of cancer-related pain with long-term use. Furthermore, patients who kept using the study medication did not seek to increase their dose of this or other pain-relieving medication over time	Johnson JR, Lossignol D, Burnell-Nugent M, Fallon MT (2013) An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. J Pain Symptom Manage. 46(2):207-18
Pain that responds poorly to opioid therapy in patients with advanced cancer	263	Nabiximols at a low dose (1-4 sprays/day), medium dose (6-10 sprays/day), or high dose (11-16 sprays/day)	Efficacy and safety of nabiximols at the 2 lower-dose levels	Portenoy, R. K., Ganae-Motan, E. D., Allende, S., Yanagihara, R. and others. (2012). Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J.Pain. 13: 438-449

Pain in patients with advanced cancer	177 patients with cancer pain, who experienced inadequate analgesia despite chronic opioid dosing	THC:CBD extract (n = 60), THC extract (n = 58), or placebo (n = 59)	Twice as many patients taking THC:CBD showed a reduction of more than 30% from baseline pain NRS score when compared with placebo (23 [43%] vs. 12 [21%]). The associated odds ratio was statistically significant, whereas the number of THC group responders was similar to placebo (12 [23%] vs. 12 [21%]) and did not reach statistical significance.	Johnson, J. R., Burnell-Nugent, M., Lossignol, D., Ganae-Motan, E. D. and others. (2010). Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J.Pain Symptom.Manage. 39: 167-179
Cancer related pain	10	Placebo and 5, 10, 15, and 20 mg THC	Pain relief significantly superior to placebo was demonstrated at high dose levels (15 and 20 mg). At these levels, substantial sedation and mental clouding were reported.	Noyes, R., Jr., Brunk, S. F., Baram, D. A., and Canter, A. (1975). Analgesic effect of delta-9-tetrahydrocannabinol. J.Clin.Pharmacol. 15: 139-143

Chronic pain in patients with advanced cancer	43 patients with cancer-related pain experiencing inadequate analgesia despite chronic opioid dosing	Sativex(®) Long-term safety and tolerability of THC/CBD spray and THC spray	The efficacy end point of change from baseline in mean Brief Pain Inventory-Short Form scores for "pain severity" and "worst pain" domains showed a decrease (i.e., improvement) at each visit in the THC/CBD spray patients. Similarly, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 scores showed a decrease (i.e., improvement) from baseline in the domains of insomnia, pain, and fatigue. No new safety concerns associated with the extended use of THC/CBD spray arose.	Johnson, J. R., Lossignol, D., Burnell-Nugent, M., and Fallon, M. T. (2012). An Open-Label Extension Study to Investigate the Long-Term Safety and Tolerability of THC/CBD Oromucosal Spray and Oromucosal THC Spray in Patients With Terminal Cancer-Related Pain Refractory to Strong Opioid Analgesics. J.Pain Symptom.Manage.
Chemotherapy induced neuropathic pain	16 patients with established chemotherapy-induced neuropathic pain	Nabiximols	There was no statistically significant difference between the treatment and the placebo groups on the NRS-PI. A responder analysis demonstrated that there were five participants who reported a two-point or greater reduction in pain that trended toward statistical significance and the number needed to treat was five.	Lynch ME, Cesar-Rittenberg P, Hohmann AG. (2014) A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. J Pain SymptomManage. 47(1):166-173

Experimental heat pain	7 men (mean age = 22.5 years, SD = +/- 1.5) and 10 women (mean age = 23.2 years, SD = +/- 2.8).	Nabilone single doses of 0.5 and 1 mg	Nabilone did not reduce the global pain intensity experienced during tonic heat pain (all values of $p > 0.18$), also failed to potentiate the strength of descending inhibitory responses (all values of $p > 43$). Nevertheless, at the highest dose (1 mg), only for women, nabilone significantly ($p = 0.003$) dampened the temporal summation experienced during the last portion of the tonic heat pulse test (i.e., the period of time during which temporal summation is greatest).	Redmond, W. J., Goffaux, P., Potvin, S., and Marchand, S. (2008). Analgesic and antihyperalgesic effects of nabilone on experimental heat pain. Curr.Med.Res.Opin. 24: 1017-1024.
Electrically induced pain, axon reflex flare, and psychometric variables in FM patients	9 FM patients	2.5-15 mg of delta-9-THC, with a weekly increase of 2.5 mg, as long as no side effects were reported	Delta-9-THC had no effect on the axon reflex flare, whereas electrically induced pain was significantly attenuated after doses of 10-15 mg delta-9-THC ($p < 0.05$). Daily-recorded pain of the FM patients was significantly reduced ($p < 0.01$).	Schley, M., Legler, A., Skopp, G., Schmelz, M. and others. (2006). Delta-9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon reflex flare, and pain relief. Curr.Med.Res.Opin. 22: 1269-1276.

Postoperative pain	65	Single oral dose of cannabis plant extract (Cannador; Institute for Clinical Research, IKF, Berlin, Germany) (5, 10, or 15 mg)	These significant dose-related improvements in rescue analgesia requirements in the 10 mg and 15 mg groups provide a number needed to treat that is equivalent to many routinely used analgesics without frequent adverse effects.	Holdcroft, A., Maze, M., Dore, C., Tebbs, S. and others. (2006). A multicenter dose-escalation study of the analgesic and adverse effects of an oral cannabis extract (Cannador) for postoperative pain management. Anesthesiology. 104: 1040-1046.
Postoperative pain	56 patients with moderate to severe postoperative or trauma pain	1.5, 2.0, 2.5, or 3.0 mg levonantradol or placebo	Significant analgesic effects of each dose of levonantradol as compared to placebo (P less than 0.05). However, no significant dose response was observed. Side effects: Drowsiness was most frequent. Dry mouth, dizziness, "weird dreams," mild hallucinations, nervousness, apprehension and confusion occurred less frequently.	Jain, A. K., Ryan, J. R., McMahon, F. G., and Smith, G. (1981). Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. J.Clin.Pharmacol. 21: 320S-326S
Postoperative pain	40 women undergoing elective abdominal hysterectomy	Identical capsule of eitheroral delta-9-THC 5 mg (n=20) or placebo (n=20)	There were no significant differences in mean (95% confidence interval of the difference) SPID at 6 h between the groups [placebo 7.9, delta-9-THC 4.3(-1.8 to 9.0)cm h on movement; placebo 8.8, delta-9-THC 4.9(-0.2 to 8.1)cm h at rest] and time to rescue analgesia [placebo 217, delta-9-THC 163(-22 to 130)min].	Buggy, D. J., Toogood, L., Maric, S., Sharpe, P. and others. (2003). Lack of analgesic efficacy of oral delta-9-tetrahydrocannabinol in postoperative pain. Pain. 106: 169-172

Postoperative pain	41 patients (mean age 52 +/- 2 yr) undergoing gynecologic (46%), orthopedic (44%), or other (10%) surgery	1 mg (n = 11) and 2 mg (n = 9) of nabilone, ketoprofen 50 mg (n = 11) or placebo (n = 10)	Pain scores at rest and on movement were significantly higher in the 2 mg nabilone group compared to the other groups. There were no significant differences between groups with respect to episodes of nausea and vomiting, quality of sleep, sedation, euphoria, pruritus, or the number and severity of adverse events. No serious adverse event was recorded.	Beaulieu, P. (2006). Effects of nabilone, a synthetic cannabinoid, on postoperative pain. Can.J.Anaesth. 53: 769-775
Neurogenic symptoms unresponsive to standard treatment, and to quantify adverse effects	24 patients with multiple sclerosis (18), spinal cord injury (4), brachial plexus damage (1), and limb amputation due to neurofibromatosis (1)	Whole-plant extracts of delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), 1:1 CBD:THC, or matched placebo (2.5-120 mg/24 hours)	Pain relief associated with both THC and CBD was significantly superior to placebo. Impaired bladder control, muscle spasms and spasticity were improved by CME in some patients with these symptoms. Three patients had transient hypotension and intoxication with rapid initial dosing of THC-containing CME.	Wade, D. T., Robson, P., House, H., Makela, P. and others. (2003). A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin.Rehabil. 17: 21-29
Fibromyalgia (FM)	56	Cannabis: the route of administration was smoking (54%), oral (46%) and combined (43%)	After 2 hours of cannabis use, VAS scores showed a statistically significant ($p<0.001$) reduction of pain and stiffness, enhancement of relaxation, and an increase in somnolence and feeling of well being.	Fiz, J., Duran, M., Capella, D., Carbonell, J. and others. (2011). Cannabis use in patients with fibromyalgia: effect on symptoms relief and health-related quality of life. PLoS.One. 6: e18440

Fibromyalgia (FM)	40	Nabilone	Effect of Nabilone on Pain and Quality of Life in Patients With Fibromyalgia	Winnipeg Regional Health Authority; Valeant Canada Limited. A trial assessing the effect of nabilone on pain and quality of life in patients with fibromyalgia. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00272207. Accessed April 7, 2014
Fibromyalgia (FM)	28 FM patients who were cannabis users and 28 non-users	Cannabis: smoking (54%), oral (46%) and combined (43%)	After 2 hours of cannabis use, VAS scores showed a statistically significant ($p<0.001$) reduction of pain and stiffness, enhancement of relaxation, and an increase in somnolence and feeling of well being. The mental health component summary score of the SF-36 was significantly higher ($p<0.05$) in cannabis users than in non-users. No significant differences were found in the other SF-36 domains, in the FIQ and the PSQI.	Fiz, J., Duran, M., Capella, D., Carbonell, J. and others. (2011). Cannabis use in patients with fibromyalgia: effect on symptoms relief and health-related quality of life. PLoS.One. 6: e18440.-
Headache	128 (survey)	Marijuana, hashish, alcoholic tincture, Marinol (5 cases)		Napchan, U., Buse, D. C., and Loder, E. W. (2011). The use of marijuana or synthetic cannabinoids for the treatment of headache. Headache. 51: 502-505.

Cluster headache refractory to multiple acute and preventive medications	1	Marijuana, dronabinol	Successfully aborted attacks with recreational marijuana use; subsequent use of dronabinol provided equally effective pain relief.	Robbins, M. S., Tarshish, S., Solomon, S., and Grosberg, B. M. (2009). Cluster attacks responsive to recreational cannabis and dronabinol. Headache. 49: 914-916.
Cluster headache (CH) attacks	139	Marijuana	Among the 27 patients (19.4% of the total cohort) who had tried cannabis to treat CH attacks, 25.9% reported some efficacy, 51.8% variable or uncertain effects, and 22.3% negative effects. Cannabis use is very frequent in CH patients, but its efficacy for the treatment of the attacks is limited.	Leroux, E., Taifas, I., Valade, D., Donnet, A. and others. (2012). Use of cannabis among 139 cluster headache sufferers. Cephalalgia. 33: 208-213.
Medication overuse headache (MOH)	30 MOH patients	Nabilone 0.5 mg/day versus ibuprofen 400 mg	Improvements from baseline were observed with both treatments. However, nabilone was more effective than ibuprofen in reducing pain intensity and daily analgesic intake ($p < 0.05$); moreover, nabilone was the only drug able to reduce the level of medication dependence (-41 %, $p < 0.01$) and to improve the quality of life ($p < 0.05$). Side effects were uncommon, mild and disappeared when nabilone was discontinued.	Pini LA, Guerzoni S, Cainazzo MM, Ferrari A, Sarchielli P, Tiraferri I, Ciccarese M, Zappaterra M (2012) Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. J Headache Pain. 13(8):677-84

Spasticity of spinal cord injured persons	43 questionnaires of spinal cord injured persons	Various	The study suggests the need to examine the relationship between measurable and reported changes in spasticity.	Malec, J., Harvey, R. F., and Cayner, J. J. (1982). Cannabis effect on spasticity in spinal cord injury. Arch.Phys.Med.Rehabil. 63: 116-118.
Spasticity and pain due to spinal cord injury		Comparing 5 mg delta-9-tetrahydrocannabinol (THC) p.o., 50 mg codeine p.o., and placebo	Delta-9-THC and codeine both had an analgesic effect in comparison with placebo. Only delta-9-THC showed a significant beneficial effect on spasticity.	Maurer, M., Henn, V., Dittrich, A., and Hofmann, A. (1990). Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. Eur.Arch.Psychiatry Clin.Neurosci. 240: 1-4.
Spasticity in people with spinal cord injury(SCI)	12	Nabilone or placebo during the first 4-week period (0.5mg once a day with option to increase to 0.5mg twice a day)	There was a significant decrease on active treatment for the Ashworth in the most involved muscle (mean difference +/- SD, .909+/-.85; P=.003), as well as the total Ashworth score (P=.001). There was no significant difference in other measures. Side effects were mild and tolerable.	Pooyania, S., Ethans, K., Szturm, T., Casey, A. and others. (2010). A randomized, double-blinded, crossover pilot study assessing the effect of nabilone on spasticity in persons with spinal cord injury. Arch.Phys.Med.Rehabil. 91: 703-707
Spasticity in people with spinal cord injury(SCI)	12	Nabilone or placebo		University of Manitoba, Valeant Canada Limited. Randomized double blind cross over study for nabilone in spasticity in spinal cord injury persons. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00623376. Accessed April 7, 2014.

SCI	Twenty-five patients with SCI (three-phase study), individual dose adjustment, each consisting of 6 weeks	Oral THC (starting with a single dose of 10 mg), rectal THC-HS, placebo. Mean daily doses were 31 mg with THC and 43 mg with THC-HS.	Mean SSS for THC decreased significantly from 16.72 (+/-7.60) at baseline to 8.92 (+/-7.14) on day 43. Similar improvement was seen with THC-HS.	Hagenbach, U., Luz, S., Ghafoor, N., Berger, J. M. and others. (2007). The treatment of spasticity with Delta9-tetrahydrocannabinol in persons with spinal cord injury. Spinal Cord. 45: 551-562.
Spasticity as a disabling complication of multiple sclerosis.	572, 19 weeks	Sativex or placebo (Phase III)	Intention-to-treat (ITT) analysis showed a highly significant difference in favour of nabiximols (P=0.0002). Secondary end-points of responder analysis, Spasm Frequency Score, Sleep Disturbance NRS Patient, Carer and Clinician Global Impression of Change were all significant in favour of nabiximols	Novotna, A., Mares, J., Ratcliffe, S., Novakova, I. and others. (2011). A randomized, double-blind, placebocontrolled, parallel-group, enriched-design study of nabiximols* (Sativex((R))), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. Eur.J.Neurol. 18: 1122-1131

Infantile spasms (IS) and Lennox-Gastaut syndrome (LGS)	117 parents of children with epilepsy (including 53 with IS or LGS) who had administered CBD products to their children	CBD products	Perceived efficacy and tolerability were similar across etiologic subgroups. Eighty-five percent of all parents reported a reduction in seizure frequency, and 14% reported complete seizure freedom. Reported side effects were far less common during CBD exposure, with the exception of increased appetite (30%). A high proportion of respondents reported improvement in sleep (53%), alertness (71%), and mood (63%) during CBD therapy.	Hussain SA, Zhou R, Jacobson C, Weng J, Cheng E, Lay J, Hung P, Lerner JT, Sankar R (2015) Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: A potential role for infantile spasms and Lennox-Gastaut syndrome. Epilepsy Behav. 47:138-41
Spasticity in multiple sclerosis		Delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) [Sativex®]	A significantly greater proportion of THC/CBD than placebo recipients achieved a ≥ 30% reduction (a clinically relevant reduction) in spasticity severity. The efficacy of THC/CBD has been also shown in at least one everyday clinical practice study (MOVE 2). THC/CBD was generally well tolerated in clinical trials.	Syed YY, McKeage K, Scott LJ. (2014) Delta-9-tetrahydrocannabinol/cannabidiol (Sativex®): a review of its use in patients with moderate to severe spasticity due to multiple sclerosis. Drugs. 74(5):563-78

Moderate to severe multiple sclerosis spasticity (MSS) resistant to other medications	276	Nabiximols (Sativex®)	After 1 month, nabiximols provided relief of resistant MSS in 74.6% of patients according to specialist assessment; mean spasticity 0-10 numerical rating scale (NRS) score decreased from 6.1 ± 1.8 to 5.2 ± 2.0 points; in patients with NRS improvement ≥20% mean NRS score decreased by 40%. After 3 months, 55.3% of patients had continued to use nabiximols and the mean NRS score had decreased by 25% from baseline. 17% of patients reported adverse events	Flachenecker P, Henze T, Zettl UK. (2014) Nabiximols (THC/CBD oromucosal spray, Sativex®) in clinical practice--results of a multicenter, non-interventional study (MOVE 2) in patients with multiple sclerosis spasticity. Eur Neurol. 71(5-6):271-9
Moderate to severe multiple sclerosis spasticity (MSS)	52 patients	Nabiximols (Sativex®)	The mean spasticity numerical rating scale (NRS, 0-10) score decreased significantly from 6.0 ± 1.8 points at MOVE 2 baseline to 4.8 ± 1.9 points after 1 month and remained on this level after 12 months (4.5 ± 2.0 points); in patients classified as 'initial responders' (≥20% NRS improvement after 1 month) similar results were found (baseline: 6.3 ± 1.4 points; after 1 month: 4.0 ± 1.0 points; after 12 months: 4.3 ± 1.9 points). The majority of patients (84%) did not report adverse events.	Flachenecker P, Henze T, Zettl UK. (2014) Long-term effectiveness and safety of nabiximols (tetrahydrocannabinol/cannabidiol oromucosal spray) in clinical practice. Eur Neurol. 72(1-2):95-102

Moderate to severe multiple sclerosis spasticity (MSS)	300 patients from 42 specialized MS centers across Germany	Nabiximols (Sativex®)	Sativex provided relief of MS-related spasticity in the majority of patients who were previously resistant to treatment. In addition, clear improvements were noted in MS spasticity-associated symptoms (e.g., sleep quality, bladder function and mobility), activities of daily living and QoL. Sativex was generally well tolerated.	Flachenecker P (2013) A new multiple sclerosis spasticity treatment option: effect in everyday clinical practice and cost-effectiveness in Germany. Expert Rev Neurother. 13(3 Suppl 1):15-9
Spasticity among patients with multiple sclerosis (MS)	50 patients (42% male) with a median age 47.8 years (25.6-76.8); 38% were diagnosed with primary progressive MS, 44% with secondary progressive MS, and 18% with relapsing-remitting MS	Inhaled THC/CBD	THC/CBD was effective in 80% of patients at a median dose of 5 (2-10) inhalations/day. The adverse event profile consisted of dizziness (11 patients), somnolence (6), muscle weakness (7), oral discomfort (2), diarrhoea (3), dry mouth (2), blurred vision (2), agitation (1), nausea (1), and paranoid ideation (1).	Lorente Fernández L, Monte Boquet E, Pérez-Miralles F, Gil Gómez I, Escutia Roig M, Boscá Blasco I, Poveda Andrés JL,Casanova-Estruch B (2014) Clinical experiences with cannabinoids in spasticity management in multiple sclerosis. Neurologia. 29(5):257-60

MS with muscle spasticity	630 patients with stable MS with muscle spasticity from 33 UK centres, 15 week and 12 months follow up	Oral Delta(9)-tetrahydrocannabinol (Delta(9)-THC) (Dronabinol, 2.5 mg), cannabis extract (2.5 mg of D9 -THC equivalent, 1.25 mg of CBD, and ,5% other cannabinoids per capsule), or placebo.	There was suggestive evidence for treatment effects of Delta(9)-THC on some aspects of disability. There were no majorsafety concerns. Overall, patients felt that these drugs were helpful in treating their disease.	Zajicek, J., Fox, P., Sanders, H., Wright, D. and others. (2003). Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet. 362: 1517-1526/ Zajicek, J. P., Sanders, H. P., Wright, D. E., Vickery, P. J. and others. (2005). Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J.Neurol.Neurosurg.Psychiatry. 76: 1664-1669
Safety in spasticity in multiple sclerosis	33 patients (60% female) aged 33-68 years and a mean disease duration of 6.6 years	Nabiximols (Sativex®)	THC:CBD oromucosal spray did not adversely influence standard driving ability in patients with moderate to severe MS spasticity. No additional safety concerns were identified in the registry studies which included findings from patients who have been treated for prolonged periods (in the German/UK registry 45% of patients had >2 years exposure).	Rekand T. (2014) THC:CBD spray and MS spasticity symptoms: data from latest studies. Eur Neurol. 71 Suppl 1:4-9

Course of progressive multiple sclerosis	498 patients	Dronabinol or placebo for 36 months; Maximum dose was 28 mg per day, titrated against bodyweight and adverse effects.	Dronabinol has no overall effect on the progression of multiple sclerosis in the progressive phase.	Zajicek J, Ball S, Wright D, Vickery J, Nunn A, Miller D, Gomez Cano M, McManus D, Mallik S, Hobart J; CUPID investigator group. (2013) Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial. Lancet Neurol. 12(9):857-65
Range of symptoms due to multiple sclerosis (MS)	160 outpatients with MS	Cannabis-based medicinal extract (CBME) (Sativex) containing equal amounts of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) at a dose of 2.5-120 mg of each daily, in divided doses.	Reduced from mean (SE) 74.36 (11.1) to 48.89 (22.0) following CBME and from 74.31 (12.5) to 54.79 (26.3) following placebo [ns]. Spasticity VAS scores were significantly reduced by CBME (Sativex) in comparison with placebo (P =0.001).	Wade, D. T., Makela, P., Robson, P., House, H. and others. (2004). Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebocontrolled study on 160 patients. Mult.Scler. 10: 434-441

Taste and smell (chemosensory)perception as well as appetite, caloric intake, and quality of life (QOL) for cancer patients with chemosensory alterations	21 patients completed the trial	THC (2.5 mg, Marinol(®); Solvay Pharma Inc.) or placebo oral capsules twice daily for 18 days	Compared with placebo, THC-treated patients reported improved (P = 0.026) and enhanced (P < 0.001) chemosensory perception and food 'tasted better' (P = 0.04). Premeal appetite (P = 0.05) and proportion of calories consumed as protein increased compared with placebo (P = 0.008). THC-treated patients reported increased quality of sleep (P = 0.025) and relaxation (P = 0.045).	Brisbois, T. D., de Kock, I. H., Watanabe, S. M., Mirhosseini, M. and others. (2011). Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. Ann.Oncol. 22: 2086-2093
Symptoms associated with multiple sclerosis (MS), poorly controlled spasticity	57	Cannabis-extract capsules standardized to 2.5 mg tetrahydrocannabinol (THC) and 0.9 mg cannabidiol (CBD) each. Drug escalation phase from 15 to maximally 30 mg THC by 5 mg	No statistically significant differences associated with active treatment compared to placebo, but trends in favour of active treatment were seen for spasm frequency, mobility and getting to sleep.	Vaney, C., Heinzel-Gutenbrunner, M., Jobin, P., Tschopp, F. and others. (2004). Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. Mult.Scler. 10: 417-424

Spasticity in multiple sclerosis	37	Smoked cannabis	Reduction in patient scores on the modified Ashworth scale by an average of 2.74 points more than placebo ($p < 0.0001$). In addition, treatment reduced pain scores on a visual analogue scale by an average of 5.28 points more than placebo ($p = 0.008$).	Corey-Bloom, J., Wolfson, T., Gamst, A., Jin, S. and others. (2012). Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. CMAJ. 184: 1143-1150
Spasticity caused by multiple sclerosis	189	Oromucosal cannabis-based medicine(CBM), 6 weeks	The primary efficacy analysis on the intention to treat (ITT) population showed the active preparation to be significantly superior ($P = 0.048$). 40% of subjects achieved >30% benefit ($P = 0.014$).	Collin, C., Davies, P., Mutiboko, I. K., and Ratcliffe, S. (2007). Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. Eur.J.Neurol. 14: 290-296
Spasticity caused by multiple sclerosis	30	Medicinal Cannabis	Assessment of Reduction in spasticity as indicated by the: Ashworth Spasticity Scale, Timed 25-ft Walk, and Grooved Pegboard Test.	Center for Medicinal Cannabis Research. Short-term effects of medicinal cannabis therapy on spasticity in multiple sclerosis. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00248378. Accessed April 7, 2014

Spasticity and other symptoms in multiple sclerosis	337 subjects with MS spasticity not fully relieved with current anti-spasticity therapy	Sativex and placebo	The per protocol (PP) population (79% of subjects) change in NRS score and responder analyses (> or =30% improvement from baseline) were both significantly superior for Sativex, compared with placebo: -1.3 versus -0.8 points (change from baseline, p=0.035); and 36% versus 24% (responders, p=0.040).	Collin C, Ehler E,Waberzinek G, et al. (2010) A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. Neurol Res. 2010;32(5):451-459
Spasticity and other symptoms in multiple sclerosis	137 MS patients with symptoms not controlled satisfactorily using standard drugs	Oromucosal cannabis-based medicine(CBM), average of 434 days	Long-term use of an oromucosal CBM (Sativex) maintains its effect in those patients who perceive initial benefit.	Wade, D. T., Makela, P. M., House, H., Bateman, C. and others. (2006). Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. Mult.Scler. 12: 639-645
Symptoms associated with multiple sclerosis (MS)	279	Oral cannabis extract (CE) or placebo.	The rate of relief from muscle stiffness after 12 weeks was almost twice as high with CE than with placebo (29.4% vs. 15.7%; OR 2.26; 95% CI 1.24 to 4.13; p=0.004, one sided).	Zajicek, J. P., Hobart, J. C., Slade, A., Barnes, D. and others. (2012). MUltiple Sclerosis and Extract of Cannabis: results of the MUSEC trial. J.Neurol.Neurosurg.Psychiatry. 83: 1125-1132

Symptoms associated with multiple sclerosis (MS)	72 subjects (36%) reported ever having used cannabis for any purpose; 29 respondents (14%) reported continuing use of cannabis for symptom treatment.	Medical cannabis	The symptoms reported by medical cannabis users to be most effectively relieved were stress, sleep, mood, stiffness/spasm, and pain.	Clark, A. J., Ware, M. A., Yazer, E., Murray, T. J. and others. (2004). Patterns of cannabis use among patients with multiple sclerosis. Neurology. 62: 2098-2100.
Symptoms associated with multiple sclerosis (MS)	16 patients with MS	Oral Delta(9)-Tetrahydrocannabinol (THC) and Cannabis sativa plant extract	Both drugs were safe, but adverse events were more common with plant-extract treatment. Compared with placebo, neither THC nor plant-extract treatment reduced spasticity. Both THC and plant-extract treatment worsened the participant's global impression.	Killestein J, Hoogervorst ELJ, ReifM, et al. (2002) Safety, tolerability, and efficacy of orally administered cannabinoids in MS. Neurology. 2002; 58(9):1404-1407.

Symptoms associated with multiple sclerosis (MS)		Smoked cannabis		Hobart JC, Zajicek JP. Cannabis as a symptomatic treatment for MS: Clinically meaningful MUSEC to the stiffness and walking problems of people with MS. Paper presented at: 28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis; October 10-13, 2012; Lyon: France. Mult Scler. 2012; 18(4 suppl 1):247
Symptoms associated with multiple sclerosis (MS)		Cannabis extract		Zajicek J, Reif M, Schnelle M. Cannabis extract in the treatment of muscle stiffness and other symptoms in multiple sclerosis—Results of the MUSEC study. Paper presented at: 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis; September 9-12, 2009; Dusseldorf: Germany. Mult Scler. 2009;15(9) (suppl S):S274
Symptoms associated with multiple sclerosis (MS)		Orally administred cannabinoids		Killestein J, Hoogervorst ELJ, Kalkers NF, et al. The effects of orally administred cannabinoids in multiple sclerosis patients: a pilot study. Mult Scler. 2000;6(1 suppl 1):S28 doi

Symptoms associated with multiple sclerosis (MS)		Cannabis extract		Zajicek J, Reif M, Schnelle M; UK MUSEC Study Investigators. Cannabis extract in the treatment of muscle stiffness and other symptoms in multiple sclerosis – results of the MUSEC study. Paper presented at: IACM5th Conference on Cannabinoids in Medicine; October 2-3, 2009; Cologne, Germany
Symptoms associated with multiple sclerosis (MS)		Sativex		Collin C, Ambler Z, Kent R, McCalla R. A randomised controlled study of Sativex® in patients with symptoms of spasticity due to multiple sclerosis. Paper presented at: 22nd Congress of the ECTRIMS; September 27-30, 2006; Madrid, Spain.
Symptoms associated with multiple sclerosis (MS)		Sativex		Robson P,Wade D, Makela P, House H, Bateman C. Cannabis-based medicinal extract (Sativex) produced significant improvements in a subjective measure of spasticity which were maintained on long-term treatment with no evidence of tolerance. Paper presented at: IACM 3rd Conference on Cannabinoids in Medicine; September 9-10, 2005; Leiden, the Netherlands

Progression of MS	493 subjects with primary or secondary progressive, but not relapse-remitting, MS	Orally administered Δ9-THC	Found no evidence to support an effect of Δ9-THC on MS progression, as measured by using either the Expanded Disability Status Scale or the Multiple Sclerosis Impact Scale 29 (MSIS-29). However, the authors concluded that there was some evidence to suggest a beneficial effect in participants who were at the lower end of the disability scale at the time of patient enrolment.	http://sites.pcmd.ac.uk/cnrg/cupid.php The CUPID (Cannabinoid Use in Progressive Inflammatory Brain Disease) study
Urge incontinence episodes without affecting voiding in patients with multiple sclerosis	630 (three groups)	Oral administration of cannabis extract, Delta(9)-tetrahydrocannabinol (THC) or matched placebo	Both active treatments showed significant effects over placebo (cannabis extract, p=0.005; THC, p=0.039). Adjusted episode rate (i.e. correcting for baseline imbalance) from baseline to the end of treatment: cannabis extract, 38%; THC, 33%; and placebo, 18%.	Freeman, R. M., Adekanmi, O., Waterfield, M. R., Waterfield, A. E. and others. (2006). The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS). Int.Urogynecol.J.Pelvic.Floor.Dysfunct. 17: 636-641

Lower urinary tract symptoms (LUTS) in patients with multiple sclerosis (MS)	21	Extracts containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD; 2.5 mg of each per spray) for eight weeks followed by THC-only (2.5 mg THC per spray) for a further eight weeks	Patient self-assessment of pain, spasticity and quality of sleep improved significantly (P <0.05, Wilcoxon's signed rank test) with pain improvement continuing up to median of 35 weeks.	Brady, C. M., DasGupta, R., Dalton, C., Wiseman, O. J. and others. (2004). An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. Mult.Scler. 10: 425-433
Multiple sclerosis	420/673 eligible subjects (response rate 62%) completed questionnaires	Medical marijuana	Subjective improvements in symptom experience were reported by the majority of people with MS who currently use cannabis.	Page, S. A., Verhoef, M. J., Stebbins, R. A., Metz, L. M. and others. (2003). Cannabis use as described by people with multiple sclerosis. Can.J.Neurol.Sci. 30: 201-205.
Multiple sclerosis	6 men and eight women with multiple sclerosis	Medical marijuana (ranged from very infrequent to very regular)	The perceived benefits of use were consistent with previous reports in the literature: reduction in pain, spasms, tremors, nausea, numbness, sleep problems, bladder and bowel problems, and fatigue and improved mood, ability to eat and drink, ability to write, and sexual functioning. Adverse effects included problems with cognition, balance, and fatigue and the feeling of being high.	Page, S. A. and Verhoef, M. J. (2006). Medicinal marijuana use: experiences of people with multiple sclerosis. Can.Fam.Physician. 52: 64-65

Appetite and quality of life (QOL) in patients with cancer-related anorexia-cachexia syndrome (CACS)	289 patients screened, 243 were randomly assigned and 164 (CE, 66 of 95 patients; THC, 65 of 100 patients; and PL, 33 of 48 patients) completed treatment	Cannabis extract (CE), delta-9-tetrahydrocannabinol (THC), and placebo (PL).	Intent-to-treat analysis showed no significant differences between the three arms for appetite, QOL, or cannabinoid-related toxicity.	Strasser, F., Luftner, D., Possinger, K., Ernst, G. and others. (2006). Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. J.Clin.Oncol. 24: 3394-3400
Food intake and body weight	6 adult male research volunteers, in two groups of three subjects each, 13 days	Two cigarettes containing active marijuana (2.3% delta 9 THC) or placebo per day	Smoked active marijuana significantly increased total daily caloric intake by 40%.	Foltin, R. W., Fischman, M. W., and Byrne, M. F. (1988). Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. Appetite. 11: 1-14

Effects across a range of behaviors: eating topography, mood, cognitive performance, physiologic measures, and sleep.	10 HIV(+) marijuana smokers	Dronabinol (5 and 10 mg) and marijuana (2.0% and 3.9% THC) dose was administered 4 times daily for 4 days	As compared with placebo, marijuana and dronabinol dose dependently increased daily caloric intake and body weight in HIV-positive marijuana smokers. Effects of marijuana and dronabinol were comparable, except that only marijuana (3.9% THC) improved ratings of sleep.	Haney, M., Gunderson, E. W., Rabkin, J., Hart, C. L. and others. (2007). Dronabinol and marijuana in HIV-positive marijuana smokers. Caloric intake, mood, and sleep. J.Acquir.Immune.Defic.Syndr. 45: 545-554
Appetite and quality of life (QOL) in patients with cancer-related anorexia-cachexia syndrome (CACS)	164	CE (standardized for 2.5 mg THC and 1 mg cannabidiol) or THC (2.5 mg) or PL orally, twice daily for 6 weeks	Intent-to-treat analysis showed no significant differences between the three arms for appetite, QOL, or cannabinoid-related toxicity. Increased appetite was reported by 73%, 58%, and 69% of patients receiving CE, THC, or PL, respectively.	Strasser, F., Luftner, D., Possinger, K., Ernst, G. and others. (2006). Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. J.Clin.Oncol. 24: 3394-3400
Anorexia due to advanced cancer	19	THC 2.5 mg p.o. t.i.d. one hour after meals for four weeks	Thirteen patients reported an improved appetite	Nelson, K., Walsh, D., Deeter, P., and Sheehan, F. (1994). A phase II study of delta-9-tetrahydrocannabinol for appetite stimulation in cancer-associated anorexia. J.Palliat.Care. 10: 14-18

Palliating cancer-associated anorexia	469	Oral megestrol acetate 800 mg/d liquid suspension plus placebo, oral dronabinol 2.5 mg twice a day plus placebo, or both agents	In the doses and schedules we studied, megestrol acetate provided superior anorexia palliation among advanced cancer patients compared with dronabinol alone. Combination therapy did not appear to confer additional benefit.	Jatoi, A., Windschitl, H. E., Loprinzi, C. L., Sloan, J. A. and others. (2002). Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. J.Clin.Oncol. 20: 567-573
Anorexia nervosa (AN)	11 female patients	Δ9-THC in daily doses from 7.5 mg (2.5 mg, t.i.d.) to a maximum of 30 mg (10 mg, t.i.d.), 90 min before meals, for a period of two weeks.	Δ9-THC produced a weight gain equivalent to the active placebo (diazepam)	Gross, H., Ebert, M. H., Faden, V. B., Goldberg, S. C. and others. (1983). A double-blind trial of delta 9-tetrahydrocannabinol in primary anorexia nervosa. J.Clin.Psychopharmacol. 3: 165-171
Severe, longstanding anorexia nervosa (AN)	25 women over 18 years with AN of at least 5 years duration	Dronabinol, 2.5 mg twice daily for 4 weeks and matching placebo for 4 weeks, separated by a 4-week wash-out period.	During dronabinol treatment, participants gained 0.73 kg ($t = 2.86$, $df = 22$, $p < 0.01$) above placebo without significant psychotropic adverse events.	Andries A, Frystyk J, Flyvbjerg A, Støving RK. Dronabinol in severe, enduring anorexia nervosa: a randomized controlled trial. Int J Eat Disord. 2014 Jan;47(1):18-23

Anorexia and disturbed behavior in patients with Alzheimer's disease	15 patients, 6 weeks	Dronabinol	Body weight of study subjects increased more during the dronabinol treatment than during the placebo periods.Dronabinol treatment decreased severity of disturbed behavior and this effect persisted during the placebo period in patientswho received dronabinol first.	Volicer, L., Stelly, M., Morris, J., McLaughlin, J. and others. (1997). Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. Int.J.Geriatr.Psychiatry. 12: 913-919
Weight loss		Placebo, 5 mg rimonabant, or 20mg rimonabant once daily in addition to a mild hypocaloric diet (600 kcal/day deficit)	Weight loss at 1 year was significantly greater in patients treated with rimonabant 5 mg (mean -3.4 kg [SD 5.7]; p=0.002 vs placebo) and 20 mg (-6.6 kg [7.2]; p<0.001 vs placebo) compared with placebo (-1.8 kg [6.4]). Significantly morepatients treated with rimonabant 20 mg than placebo achieved weight loss of 5% or greater (p<0.001) and 10% or greater (p<0.001).	Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rössner S; RIO-Europe Study Group. (2005) Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascularrisk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet. 2005 Apr 16-22;365(9468):1389-97

Caloric intake, sleep quality in HIV-positive marijuana smokers	7, marijuana 4.2 ± 2.3 days/week,	Two 16-day stays, dronabinol (10 mg QID) in one stay and placebo in the other	Despite sustained increases in self-reported food cravings, dronabinol only increased caloric intake in the initial 8 days of dosing. Similarly, sleep quality was improved only in the first 8 days of dosing. Dronabinol's mood-enhancing effects were sustained across the 16-day inpatient stay. Dronabinol was well tolerated, causing few negative subjective or cognitive effects.	Bedi, G., Foltin, R. W., Gunderson, E. W., Rabkin, J. and others. (2010). Efficacy and tolerability of high-dose dronabinol maintenance in HIV-positive marijuana smokers: a controlled laboratory study. Psychopharmacology (Berl). 212: 675-686.
HIV wasting syndrome	39 completed the planned 12 weeks of study visits	Dronabinol 2.5 mg twice/day (D); megestrol acetate 750 mg/day (M750); megestrol acetate 750 mg/day+dronabinol 2.5 mg twice/day (M750+D); or megestrol acetate 250 mg/day+dronabinol 2.5 mg twice/day (M250+D)	The mean weight change +/- SE over 12 weeks was as follows: D, -2.0 +/- 1.3 kg; M750, +6.5 +/- 1.1 kg; M750+D, +6.0 +/- 1.0 kg; and M250+D, -0.3 +/- 1.0 kg (difference among treatment arms, p = 0.0001).	Timpone, J. G., Wright, D. J., Li, N., Egorin, M. J. and others. (1997). The safety and pharmacokinetics of singleagent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. The DATRI 004 Study Group. Division of AIDS Treatment Research Initiative. AIDS Res.Hum.Retroviruses. 13: 305-315

AIDS-related anorexia	12 HIV-infected patients who had had at least a 2.25-kg weight loss	Dronabinol 5 mg twice daily before meals or placebo	During dronabinol treatment, subjects experienced increased percent body fat (one percent, p = 0.04); decreased symptom distress (p = 0.04); and trends toward weight gain (0.5 kg, p = 0.13), increased prealbumin (29.0 mg/L, p = 0.11), and improved appetite score (p = 0.14).	Struwe M, Kaempfer SH, Geiger CJ, et al. (1997) Effect of dronabinol on nutritional status in HIV infection. Ann Pharmacother. 27(7-8):827-831
AIDS-related anorexia	139	2.5 mg dronabinol twice daily or placebo	Dronabinol was associated with increased appetite above baseline (38% vs 8% for placebo, P = 0.015), improvement in mood (10% vs -2%, P = 0.06), and decreased nausea (20% vs 7%; P = 0.05). Weight was stable in dronabinolpatients, while placebo recipients had a mean loss of 0.4 kg (P = 0.14). Of the dronabinol patients, 22% gained > or = 2 kg, compared with 10.5% of placebo recipients (P = 0.11).	Beal, J. E., Olson, R., Laubenstein, L., Morales, J. O. and others. (1995). Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J.Pain Symptom.Manage. 10: 89-97
AIDS-related anorexia	94 late-stage acquired immunodeficiency syndrome (AIDS)patients (mean CD4 count of 45/mm3), 12 months	Dronabinol orally-2.5 mg twice daily (90%) or 2.5 mg once daily (10%)	Dronabinol was associated with a VASH change at least twice baseline and stable body weight for at least 7 months	Beal, J. E., Olson, R., Lefkowitz, L., Laubenstein, L. and others. (1997). Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. J.Pain Symptom.Manage. 14: 7-14

Acute effects on caloric intake and mood in HIV(+) marijuana smokers	30 HIV(+) marijuana smokers with and without clinically significant loss of muscle mass	Dronabinol (0, 10, 20, 30 mg p.o.) and marijuana [0.0, 1.8, 2.8, 3.9% Delta(9)-tetrahydrocannabinol (THC)]	Marijuana and dronabinol significantly increased caloric intake in the low bioelectrical impedance analysis (BIA) group but not in the normal BIA group;drug effects on cognitive performance were minor	Haney, M., Rabkin, J., Gunderson, E., and Foltin, R. W. (2005). Dronabinol and marijuana in HIV(+) marijuana smokers: acute effects on caloric intake and mood. Psychopharmacology (Berl). 181: 170-178
Improvement in quality of life, disease activity and weight gain in Inflammatory bowel disease (IBD) patients	13, 3 months	Inhaled cannabis	Improvement in general health perception ($p = 0.001$), social functioning ($p = 0.0002$), ability to work ($p = 0.0005$), physical pain ($p = 0.004$) and depression ($p = 0.007$). Patients had a weight gain of 4.3 ± 2 kg during treatment (range 2-8; $p = 0.0002$) and an average rise in BMI of 1.4 ± 0.61 (range 0.8-2.7; $p = 0.002$). The average Harvey-Bradshaw index was reduced from 11.36 ± 3.17 to 5.72 ± 2.68 ($p = 0.001$).	Lahat, A., Lang, A., and Ben-Horin, S. (2012). Impact of cannabis treatment on the quality of life, weight and clinical disease activity in inflammatory bowel disease patients: a pilot prospective study. Digestion. 85: 1-8
Antiemetic effect	13 healthy volunteer with ipecac induced emesis.	Smoked marijuana cigarettes (8.4 and 16.9 mg Delta(9)-tetrahydrocannabinol [THC]) compared to antiemetic drug, ondansetron (8 mg)	Marijuana significantly reduced ratings of "queasiness" and slightly reduced the incidence of vomiting compared to placebo.	Soderpalm, A. H., Schuster, A., and de, Wit H. (2001). Antiemetic efficacy of smoked marijuana: subjective and behavioral effects on nausea induced by syrup of ipecac. Pharmacol.Biochem.Behav. 69: 343-350

Antiemetic effect		Levonantradol and Prochlorperazine		Long A,Mioduszewski J, Natale R. (1982) A randomized double-blind cross-over comparison of the antiemetic activity of levonantradol and prochlorperazine. Proc Am Soc Clin Oncol. 1: C-220.
Antiemetic effect		THC vs hydroxizine		Broder LE, Lean NL, Hilsenbeck SG. (1982) A randomized blinded clinical trial comparing delta-9-tetrahydrocannabinol (THC) and hydroxizine (HZ) as antiemetics (AE) for cancer chemotherapy (CT). Proc Am Assoc Cancer Res. ;23:514
Antiemetic effect	36 patients whose vomiting was refractory to standard antiemetic therapy	Oral delta-9-tetrahydrocannabinol (THC), 15 mg/m2, was compared to prochlorperazine (PCZ), 10 mg	THC decreased nausea and vomiting in 23 of 36 (64%) patients compared to 1 of 36 receiving PCZ. THC efficacy was not dependent on the class of antineoplastic-agent inducing the emetic symptoms, age of patients or type of sensorial change experienced.	McCabe M, Smith FP, Macdonald JS,Woolley PV, Goldberg D, Schein PS.(1988) Efficacy of tetrahydrocannabinol in patients refractory to standard antiemetic therapy. Invest New Drugs. 6(3):243-246

Antiemetic effect	38 patients receiving highly emetogenic chemotherapy regimens (70% containing cisplatin)	Butyrophenone analogue domperidone (D) versus the synthetic cannabinoid nabilone (N)	Nausea and food intake scores did not differ significantly, although there was a trend towards less nausea and an increased food intake with N. Subjectively adverse effects were more frequent with N and included drowsiness, dizziness, dry mouth, and postural hypotension. N is superior to D for the control of cytotoxic-induced emesis	Pomeroy M, Fennelly JJ, Towers M. (1986) Prospective randomized double-blind trial of nabilone versus domperidone in the treatment of cytotoxic-induced emesis. Cancer Chemother Pharmacol. 17(3): 285-288.
Antiemetic effect	18 eligible children, aged 10 months to 17 years	Nabilone versus domperidone	When taking nabilone they experienced significantly fewer vomiting episodes and less nausea, and two thirds expressed a preference for the drug. The most common side effects of treatment with nabilone were somnolence and dizziness, with one patient being disturbed by hallucinations.	Dalzell AM, Bartlett H, Lilleyman JS. (1986) Nabilone: an alternative antiemetic for cancer chemotherapy. Arch Dis Child. 61(5):502-505.
Antiemetic effect	16 patients	1 mg levonantradol, versus 10 mg prochlorperazine	There were no statistical differences in patients' responses to levonantradol and prochlorperazine. The frequency of side effects was greater with levonantradol than with prochlorperazine.	Sheidler VR, Ettinger DS, Diasio RB, Enterline JP, Brown MD. (1984) Double-blind multiple-dose crossover study of the antiemetic effect of intramuscular levonantradol compared to prochlorperazine. J Clin Pharmacol. 24(4):155-159.

Antiemetic effect		Dronabinol		Harden-Harrison MM, MunsellMF, Fisch MJ, et al. (2012) Dronabinol for the prevention of nausea from cyclophosphamide and/or adriamycin. Paper presented at: International MASCC/ISOO Symposium: Supportive Care in Cancer; June 28-30, 2012; New York, NY. Support Care Cancer. 2012;20:S209-S210.
Antiemetic effect/CINV	16	Whole-plant cannabis-based medicine (CBM) containing delta-9-tetrahydrocannabinol and cannabidiol, taken in conjunction with standard therapies in the control of CINV.	A higher proportion of patients in the CBM group experienced a complete response during the overall observation period [5/7 (71.4%) with CMB vs. 2/9 (22.2%) with placebo, the difference being 49.2% (95% CI 1%, 75%)], due to the delayed period. The incidence of AEs was higher in the CBM group (86% vs. 67%). No serious AEs were reported.	Duran M, P?rez E, Abanades S, et al. (2010) Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy induced nausea and vomiting. Br J Clin Pharmacol. 70(5):656-663
Antiemetic effect/CINV	64 patients	Dronabinol, ondansetron, or the combination	Nausea absence was significantly greater in active treatment groups (dronabinol, 71%; ondansetron, 64%; combination therapy, 53%) versus placebo (15%; $p < 0.05$ vs. placebo for all). Nausea intensity and vomiting/retching were lowest in patients treated with dronabinol.	Meiri E, Jhangiani H, Vredenburgh JJ, et al. (2007) Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Curr Med Res Opin. 23(3):533-543

Antiemetic effect/CINV		Dronabinol and prochlorperazine alone and in combination	Addition of prochlorperazine to dronabinol appeared to decrease the frequency of dysphoric effects seen with the latter agent. The combination was significantly more effective than was either single agent in controlling chemotherapy-induced nausea and vomiting.	Lane M, Vogel CL, Ferguson J, et al. (1991) Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. J Pain Symptom Manage. 6(6):352-359
Antiemetic effect/CINV	20 nonseminomatous testicular cancer patients	Nabilone (2 X 2 mg/day) or alizapride (3 X 150 mg/day) prior to beginning low-dose cisplatin chemotherapy	Patients on nabilone had significantly fewer episodes of emesis than those on alizapride (medians, 1.1 vs 2.9; p less than 0.01). Nabilone was superior to alizapride in giving complete relief from nausea (medians, 65% vs 30%; p less than 0.01), and was more effective in shortening the duration of nausea (medians, 1.3 h vs 5.1 h; p less than 0.01); however, it caused more adverse effects.	Niederle N, Sch□tte J, Schmidt CG. (1986) Crossover comparison of the antiemetic efficacy of nabilone and alizapride in patients with nonseminomatous testicular cancer receiving cisplatin therapy. Klin Wochenschr. 64(8):362-365
Antiemetic effect/CINV	24 lung cancer patients receiving cancer chemotherapy	2 mg of nabilone, or 15 mg of prochlorperazine	Nabilone was significantly superior to prochlorperazine in the reduction of vomiting episodes. Side effects, mainly vertigo, were evident in nearly half of the patients after nabilone, and three patients were withdrawn from the study due to decreased coordination and hallucinations after nabilone.	Niiranen A, Mattson K. (1985) A cross-over comparison of nabilone and prochlorperazine for emesis induced by cancer chemotherapy. Am J Clin Oncol. 8(4):336-340.

Antiemetic effect/CINV	57 cancer patients receiving chemotherapy	Low-dose levonantradol or standard-dose metoclopramide and crossed over to the other antiemetic drug in the next identical chemotherapy cycle	Patient preference for antiemetic treatment was levonantradol in 49% and metoclopramide in 22% of cases. Levonantradol treatment was accompanied by a relatively high incidence of side-effects (71%) compared with metoclopramide (29%)	HeimME, QueisserW, Altenburg HP. (1984) Randomized crossover study of the antiemetic activity of levonantradol and metoclopramide in cancer patients receiving chemotherapy. Cancer Chemother Pharmacol. 13(2):123-125
Antiemetic effect/CINV	108 patient	Levonantradol (0.5, 0.75 or 1 mg) or chlorpromazine (25 mg) prior to receiving first course of cytotoxic therapy	Levonantradol (0.5 mg) was superior to chlorpromazine (25 mg) as an anti-emetic. Both were reasonably well tolerated, although at this dose of levonantradol 22% of patients experienced dysphoric reactions. At higher doses of levonantradol the proportion of patients experiencing these reactions rose to 50%, but without a concomitant increase in antiemetic activity. Neither drug achieved satisfactory control of vomiting in patients receiving combinations containing cis-platinum.	Hutcheon AW, Palmer JB, Soukop M, et al. (1983) A randomised multicentre single blind comparison of a cannabinoid anti-emetic (levonantradol) with chlorpromazine in patients receiving their first cytotoxic chemotherapy. Eur J Cancer Clin Oncol. 19(8):1087-1090

Antiemetic effect/CINV	20 patients with advanced gynaecological cancer who received chemotherapy including cis-platinum	Nabilone 3 mg, orally three times a day, Chlorpromazine 12.5 mg given IM, 15 minutes before the start of cis-platinum	Nabilone, in comparison with chlorpromazine did not significantly reduce the number of vomiting. Ten patients preferred nabilone, 5 preferred chlorpromazine and 3 were undecided. Predominant side effects noted by patients were similar for both agents and included somnolence, dry mouth and orthostatic hypotension.	George M, Pejovic MH, Thuaire M, Kramar A, Wolff JP. (1983) [Randomized comparative trial of a new anti-emetic: nabilone, in cancer patients treated with cisplatin]. Biomed Pharmacother. 37(1):24-27
Antiemetic effect/CINV		Nabilone vs placebo		Jones SE, Durant JR, Greco FA, Robertone A. (1982) A multi-institutional phase III study of nabilone vs placebo in chemotherapy-induced nausea and vomiting. Cancer Treat Rev. 9(suppl B):45-48
Antiemetic effect/CINV		Nabilone vs placebo		Wada JK, Bogdon DL, Gunnell JC, Hum GJ, Gota CH, Rieth TE. (1982) Double-blind, randomized, crossover trial of nabilone vs placebo in cancer chemotherapy. Cancer Treat Rev. 9(suppl B):39-44
Antiemetic effect/CINV		Nabilone vs. prochlorperazine		Johansson R, Kilkku P, Groenroos M. (1982) A double-blind, controlled trial of nabilone vs. prochlorperazine for refractory emesis induced by cancer chemotherapy. Cancer Treat Rev. 9(suppl B):25-33

Antiemetic effect/CINV	55 patients harboring a variety of neoplasms and previously found to have severe nausea or emesis from antitumor drugs	Delta 9-Tetrahydrocannabinol (THC), prochlorperazine, and placebo	Nausea was absent in 40 of 55 patients receiving THC, in 8 of 55 patients receiving prochlorperazine, and in 5 of 55 in the placebo group. THC appeared to be more efficacious in controlling the emesis associated with cyclophosphamide, 5-fluorouracil, and doxorubicin and less so for nitrogen mustard and the nitrosourea.	Orr LE, McKernan JF. (1981) Antiemetic effect of delta 9-tetrahydrocannabinol in chemotherapy associated nausea and emesis as compared to placebo and compazine. J Clin Pharmacol. 21(8-9 suppl):76S-80S
Antiemetic effect/CINV	80 evaluable patients receiving chemotherapy	Nabilone versus prochlorperazine	Sixty patients (75 per cent) reported nabilone to be more effective than prochlorperazine for relief of nausea and vomiting. Of these 60 patients, 46 required further chemotherapy and continued taking nabilone as the antiemetic of choice.	Einhorn LH, Nagy C, Furnas B, Williams SD. (1981) Nabilone: an effective antiemetic in patients receiving cancer chemotherapy. J Clin Pharmacol. 21(8-9 suppl):64S-69S

Antiemetic effect/CINV	55 patients previously found to have severe nausea or emesis from antitumor drugs	Tetrahydrocannabinol (THC), prochlorperazine, and placebo	Nausea was absent in 40 of 55 patients receiving THC, eight of 55 patients receiving prochlorperazine, and five of 55 in the placebo group. The antiemetic effect of THC appeared to be more efficacious for cyclophosphamide, fluorouracil, and doxorubicin hydrochloride, and less so for mechlorethamine hydrochloride and the nitrosureas.	Orr LE, McKernan JF, Bloome B. (1980)Antiemetic effect of tetrahydrocannabinol: compared with placebo and prochlorperazine in chemotherapyassociated nausea and emesis. Arch Intern Med. 140(11):1431-1433.
Antiemetic effect/CINV	37 patients receiving cancer chemotherapy	Nabilone given at a dose of 2 mg every 12 hours versus slow-release capsules of prochlorperazine given at a dose of 10 mg every 12 hours	Eighteen of the 37 patients achieved a complete or partial elimination of symptoms: seven with nabilone alone, three with prochlorperazine alone, and eight with each drug. Nabilone appeared to be the more effective antiemetic for patients who received chemotherapy agents other than high dose DDP; it was equivalent to prochlorperazine for those who did receive high-dose DDP.	Steele N, Gralla RJ, Braun DWJr, Young CW. (1980) Double-blind comparison of the antiemetic effects of nabilone and prochlorperazine on chemotherapy-induced emesis. Cancer Treat Rep. 64(2-3):219-224
Antiemetic effect/CINV	25 patients who had failed to benefit from standard antiemetic therapy	THC versus prochlorperazine (compazine)	THC is an effective antiemetic in many patients who receive chemotherapy for cancer and for whom other antiemetics are ineffective	Sallan SE, Cronin C, Zelen M, Zinberg NE. (1980) Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. N Engl J Med. 302(3):135-138.

Antiemetic effect/CINV	116 patients (median age 61 years) receiving combined 5-fluorouracil and semustine (methyl CCNU) therapy for gastrointestinal carcinoma	THC, 15 mg orally three times a day, prochlorperazine, 10 mg orally three times a day, or placebo	The THC had superior antiemetic activity in comparison to placebo, but it showed no advantage over prochlorperazine. Central nervous system side-effects, however, were significantly more frequent and more severe with THC	Frytak S, Moertel CG, O'Fallon JR, et al. (1979) Delta-9 tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy: a comparison with prochlorperazine and a placebo. Ann Intern Med. 91(6):825-830
Antiemetic effect/CINV	34 patients with lung cancer undergoing a 3-day schedule of chemotherapy with Cyclophosphamide, Adriamycin and Etoposide	Nabilone versus Prochlorperazine	Symptom scores were significantly better for patients on nabilone for nausea, retching and vomiting (P less than 0.05). Fewer subjects vomited with nabilone (P = 0.05) and the number of vomiting episodes was lower (P less than 0.05); no patients on nabilone required additional parenteral anti-emetic.	Ahmedzai S, Carlyle DL, Calder IT, Moran F. (1983) Anti-emetic efficacy and toxicity of nabilone, a synthetic cannabinoid, in lung cancer chemotherapy. Br J Cancer. 48(5):657-663

Antiemetic effect/CINV	214 (75% of whom had previously received Compazine with varying results)	Delta-9-tetrahydrocannabinol (THC) versus prochlorperazine (Compazine); THC was administered by body surface area (BSA): BSA less than 1.4 m2 = 7.5 mg; BSA 1.4-1.8 m2 = 10- mg; and BSA greater than 1.8 m2 = 12.5 mg	There were significant drug effects with THC: less ability to concentrate (P less than 0.01), less social interaction (P less than 0.05), and less activity (P less than 0.05). There were no significant differences between the two drugs in the level of food intake or appetite.	Ungerleider JT, Andrysiak T, Fairbanks L, Goodnight J, Sarna G, Jamison K. (1982) Cannabis and cancer chemotherapy: a comparison of oral delta-9-THC and prochlorperazine. Cancer. 50(4):636-645.
Antiemetic effect/CINV		Dronabinol		Grunberg SM, MunsellMF, Morrow PKH, et al. (2012) Randomized double-blind evaluation of dronabinol for the prevention of chemotherapy-induced nausea. Paper presented at: Annual Meeting of the American Society of Clinical Oncology (ASCO); 1-5 Jun 2012; Chicago, IL. J Clin Oncol. 2012;30(15)(suppl 1):9061.

Antiemetic effect/CINV		Dronabinol versus prochlorperazine		Lane M, Vogel CL, Ferguson J, et al. (1989) Dronabinol and prochlorperazine in combination are better than either single agent alone for treatment of chemotherapy-induced nausea and vomiting. Proc Am Soc Clin Oncol. 8:326.
Antiemetic effect/CINV		Nabilone vs placebo		LevittM. (1982) Nabilone vs placebo in the treatment of chemotherapy-induced nausea and vomiting in cancer patients. Cancer Treat Rev. 9(suppl B):49-53.
Antiemetic effect/CINV		Nabilone vs prochlorperazine		Chan HS, MacLeod SM, Correia JA. (1984) Nabilone vs prochlorperazine for control of cancer chemotherapy-induced emesis in children. Proc Am Soc Clin Oncol. 3:108.
Antiemetic effect/CINV		Dronabinol (10 - 20 mg) versus Ondansetron (8 - 16 mg) or dronabinol/ondansetron (10 - 20 mg/8 - 16 mg)		Solvay Pharmaceuticals. Dronabinol versus standard ondansetron antiemetic therapy in preventing delayed-onset chemotherapy-induced nausea and vomiting. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00642512 Accessed April 7, 2014

Antiemetic effect/CINV		Delta-9-tetrahydrocannabinol (THC), prochlorperazine (PCP) and placebo		Frytak S, Moertel CG, Ofallon JR. Comparison of delta-9-tetrahydrocannabinol (THC), prochlorperazine (PCP) and placebo as anti-emetics for cancer-chemotherapy. Proc Am Assoc Cancer Res. 1979;20:391
Antiemetic effect/CINV		Dronabinol or ondansetron alone and combined		Jhangiani H, Vredenburgh JJ, Barbato L, et al. (2005) Dronabinol or ondansetron alone and combined for delayed chemotherapy-induced nausea and vomiting (CINV). Blood. 106(11, part 2):477B
Antiemetic effect/CINV		Oral THC vs prochlorperazine		McCabe M, Smith FP, Goldberg D, et al. (1981) Comparative trial of oral 9 tetrahydrocannabinol and prochlorperazine for cancer chemotherapy related nausea and vomiting. Proc Am Assoc Cancer Res and Am Soc Clin Oncol. 22:416
Antiemetic effect/CINV	113 patients	Nabilone vs prochlorperazine	When both drugs were compared, both nausea (P less than 0.01) and vomiting episodes (P less than 0.001) were significantly lower in patients given nabilone. Moreover, patients clearly favored nabilone for continued use (P less than 0.001).	Herman TS, Einhorn LH, Jones SE, et al. (1979) Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. N Engl J Med. 300(23):1295-1297

Antiemetic effect/CINV		Palonosetron plus dexamethasone with or without dronabinol		Melhem-Bertrandt AI, MunsellMF, Fisch MJ, et al. (2014) A randomized, double-blind, placebo-controlled trial of palonosetron plus dexamethasone with or without dronabinol for the prevention of chemotherapy-induced nausea and vomiting after moderately emetogenic chemotherapy [Unpublished manuscript]. 2014:1-23
Antiemetic effect/CINV	25	THC vs. prochlorperazine (compazine)		Sallan, S. E., Cronin, C., Zelen, M., and Zinberg, N. E. (1980). Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. N.Engl.J.Med. 302: 135-138

Antiemetic effect/CINV in children	30 children 3.5 to 17.8 years of age	Nabilone versus prochlorperazine	The overall rate of improvement of retching and emesis was 70% during the nabilone and 30% during the prochlorperazine treatment cycles (P = .003, chi 2 test). On completion of the trial, 66% of the children stated that they preferred nabilone, 17% preferred prochlorperazine, and 17% had no preference (P = .015, chi 2 test).	Chan HS, Correia JA, MacLeod SM. (1987) Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial. Pediatrics. 79 (6):946-952.
Antiemetic effect/CINV in children		THC vs. metoclopramide syrup and prochlorperazine tablets	THC was found to be a significantly better antinausea and antivomiting agent, but not all patients obtained relief of nausea and vomiting with THC.	Ekert, H., Waters, K. D., Jurk, I. H., Mobilia, J. and others. (1979). Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol. Med.J.Aust. 2: 657-659

Metabolic risk factors, including adiponectin levels, in high-risk patients who are overweight or obese and have dyslipidemia	1036 overweight or obese patients	Placebo or rimonabant at a dose of 5 mg or 20 mg daily for 12 months	The most frequent adverse events resulting in discontinuation of the drug were depression, anxiety, and nausea. As compared with placebo, rimonabant at a dose of 20 mg was associated with a significant (P<0.001) mean weight loss (repeated-measures method, -6.7+/-0.5 kg, and last-observation-carried-forward analyses, -5.4+/-0.4 kg), reduction in waist circumference (repeated-measures method, -5.8+/-0.5 cm, and last-observation-carried-forward analyses, -4.7+/-0.5 cm), increase in HDL cholesterol (repeated-measures method, +10.0+/-1.6 percent, and last-observation-carried-forward analyses, +8.1+/-1.5 percent), and reduction in triglycerides (repeated-measures method, -13.0+/-3.5 percent, and last-observation-carried-forward analyses, -12.4+/-3.2 percent). Rimonabant at a dose of 20 mg also resulted in an increase in plasma adiponectin levels (repeated-measures method, 57.7 percent, and last-observation-carried-forward analyses, 46.2 percent; P<0.001), for a change that was partly independent of weight loss alone.	Despres, J. P., Golay, A., and Sjostrom, L. (2005). Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N.Engl.J.Med. 353: 2121-2134

Body weight and cardiometabolic risk factors in patients who are overweight or obese	3045 obese (body mass index > or =30) or overweight (body mass index >27 and treated or untreated hypertension or dyslipidemia) adult patients	Placebo, 5 mg/d of rimonabant, or 20 mg/d of rimonabant for 1 year	At year 1, the completion rate was 309 (51%) patients in the placebo group, 620 (51%) patients in the 5 mg ofrimonabant group, and 673 (55%) patients in the 20 mg of rimonabant group. Compared with the placebo group, the 20 mg ofrimonabant group produced greater mean (SEM) reductions in weight (-6.3 [0.2] kg vs -1.6 [0.2] kg; P<.001), waist circumference (-6.1 [0.2] cm vs -2.5 [0.3] cm; P<.001), and level of triglycerides (percentage change, -5.3 [1.2] vs 7.9 [2.0]; P<.001) and a greater increase in level of high-density lipoprotein cholesterol (percentage change, 12.6 [0.5] vs 5.4 [0.7]; P<.001). Patients who were switched from the 20 mg of rimonabant group to the placebo group during year 2 experienced weight regain	Pi-Sunyer, F. X., Aronne, L. J., Heshmati, H. M., Devin, J. and others. (2006). Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA. 295: 761-775.
Weight loss	1047 overweight or obese type 2 diabetes patients	Placebo (n=348), 5 mg/day rimonabant (360) or 20 mg/day rimonabant (339) for 1 year	Weight loss was significantly greater after 1 year in both rimonabant groups than in the placebo group (placebo: -1.4 kg [SD 3.6]; 5 mg/day: -2.3 kg [4.2], p=0.01 vs placebo; 20 mg/day: -5.3 kg [5.2], p<0.0001 vs placebo).	Scheen, A. J., Finer, N., Hollander, P., Jensen, M. D. and others. (2006). Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. Lancet. 368: 1660-1672

Weight loss		Placebo, rimonabant 5 or 20 mg once daily plus a calorie-restricted diet for 2 years	Rimonabant 20 mg over 2 years promoted clinically relevant and durable weight loss and improvements incardiometabolic risk factors	Van Gaal, L. F., Scheen, A. J., Rissanen, A. M., Rossner, S. and others. (2008). Long-term effect of CB1 blockade with rimonabant on cardiometabolic risk factors: two year results from the RIO-Europe Study. Eur.Heart J. 29: 1761-1771
Weight loss	5,580 patients without diabetes (3,165 completed treatment) and 1,047 patients with diabetes (692 completed treatment)	Rimonabant (5 or 20 mg) or placebo for 1 year	In overweight/obese patients, 20 mg/day rimonabant produced weight loss and significant improvements inmultiple cardiometabolic risk factors such as waist circumference, A1C, HDL cholesterol, and triglycerides. Rimonabant was generally well tolerated, with more frequently reported adverse events being gastrointestinal, neurological, and psychiatric in nature.	Van Gaal, L., Pi-Sunyer, X., Despres, J. P., McCarthy, C. and others. (2008). Efficacy and safety of rimonabant for improvement of multiple cardiometabolic risk factors in overweight/obese patients: pooled 1-year data from the Rimonabant in Obesity (RIO) program. Diabetes Care. 31 Suppl 2: S229-S240

Weight loss	803 abdominally obese patients with atherogenic dyslipidemia	Placebo or rimonabant 20 mg/d for 1 year	Rimonabant decreased abdominal subcutaneous adipose tissue (AT) cross-sectional area by 5.1% compared to placebo (P≤0.005), with a greater reduction in visceral AT. Rimonabant significantly reduced liver fat content. Systolic (-3.3 mm Hg) and diastolic (-2.4 mm Hg) blood pressure were significantly reduced with rimonabant versus placebo (P<0.0001). Gastrointestinal, nervous system, psychiatric, and general adverse events were more common with rimonabant 20 mg.	Despres, J. P., Ross, R., Boka, G., Almeras, N. and others. (2009). Effect of rimonabant on the high-triglyceride/ low-HDL-cholesterol dyslipidemia, intraabdominal adiposity, and liver fat: the ADAGIO-Lipids trial. Arterioscler.Thromb.Vasc.Biol. 29: 416-423

Overweight/obesity in young adults	2566 young adults (1264 males and 1302 females) who had data available on cannabis use and age of initiation to use of cannabis and BMI at the 21-year follow-up (MUSP children)	Cannabis, 21-year follow-up	Multivariate analysis showed that those who had used cannabis were less likely to be categorised in the BMI $\geq$ 25 group with the least prevalence of overweight/obesity being observed in every day cannabis users (odds ratio = .2; 95% confidence interval [CI]:.1-.4).	Hayatbakhsh, M. R., O'Callaghan, M. J., Mamun, A. A., Williams, G. M. and others. (2010). Cannabis use and obesity and young adults. Am.J.Drug Alcohol Abuse. 36: 350-356.
Overweight/obesity	US adults aged 18 years or older; -	Cannabis	The prevalence of obesity is lower in cannabis users than in nonusers.	Le Strat, Y. and Le Foll, B. (2011). Obesity and cannabis use: results from 2 representative national surveys. Am.J.Epidemiol. 174: 929-933

Diabetes	10 896 adults in four groups: non-marijuana users (61.0%), pastmarijuana users (30.7%), light (one to four times/month) (5.0%) and heavy (more than five times/month) current marijuana users(3.3%)	Cannabis	Marijuana users had a lower age-adjusted prevalence of DM compared to non-marijuana users (OR 0.42, 95% CI 0.33 to 0.55; p<0.0001). The prevalence of elevated C reactive protein (>0.5 mg/dl) was significantly higher (p<0.0001) among non-marijuana users (18.9%) than among past (12.7%) or current light (15.8%) or heavy (9.2%) users. In a robust multivariate model controlling for socio-demographic factors, laboratory values and comorbidity, the lower odds of DM among marijuana users significant (adjusted OR 0.36, 95% CI 0.24 to 0.55; p<0.0001).	Rajavashisth, T. B., Shaheen, M., Norris, K. C., Pan, D. and others. (2012). Decreased prevalence of diabetes in marijuana users: cross-sectional data from the National Health and Nutrition Examination was Survey (NHANES) III. BMJ Open. 2: e000494-

GI transit, gastric volume and satiation	30 healthy volunteers	Dronabinol (DRO) and placebo (PLA)	There was an overall retardation of gastric emptying with DRO (P = 0.018); this was more pronounced in females (P = 0.011), than in males (P = 0.184). No significant treatment differences were detected for gastric volumes, MTV, post-Ensure(R) symptoms, small bowel and colonic transit. Fasting gastric volume was greater in males receiving DRO compared with PLA (238 +/- 17 vs 185 +/- 16, P = 0.04).	Esfandyari, T., Camilleri, M., Ferber, I., Burton, D. and others. (2006). Effect of a cannabinoid agonist on gastrointestinal transit and postprandial satiation in healthy human subjects: a randomized, placebo-controlled study. Neurogastroenterol.Motil. 18: 831-838
Colonic motility and sensation	52 volunteers	Single dose of 7.5 mg DRO or PLA postoperative with concealed allocation	DRO, relaxes the colon and reduces postprandialcolonic motility and tone. Increase in sensation ratings to distension in the presence of relaxation of the colon suggests central modulation of perception.	Esfandyari, T., Camilleri, M., Busciglio, I., Burton, D. and others. (2007). Effects of a cannabinoid receptor agonist on colonic motor and sensory functions in humans: a randomized, placebo-controlled study. Am.J.Physiol Gastrointest.Liver Physiol. 293: G137-G145

Colonic motility and sensation in patients with IBS	75 individuals with IBS (35 with IBS with constipation, 35 with IBS with diarrhea, and with 5 IBS alternating)	1 dose of placebo or 2.5 mg or 5.0 mg dronabinol	In all patients, dronabinol decreased fasting proximal left colonic MI compared with placebo (overall P = .05; for 5 mg dronabinol, P = .046), decreased fasting distal left colonic MI (overall P = .08; for 5 mg, P = .13), and increased coloniccompliance (P = .058).	Wong, B. S., Camilleri, M., Busciglio, I., Carlson, P. and others. (2011). Pharmacogenetic trial of a cannabinoid agonist shows reduced fasting colonic motility in patients with nonconstipated irritable bowel syndrome. Gastroenterology. 141: 1638-1647
Gut transit in patients with IBS	36 IBS-D volunteers	Twice per day PLA (n = 13), DRO 2.5 mg (n = 10), or DRO 5 mg (n = 13) for 2 days	Overall, DRO 2.5 or 5 mg twice per day for 2 days had no effect on gut transit in IBS-D. There appears to be a treatment-by-genotype effect, whereby DRO preferentially delays colonic transit in those with the CNR1 rs806378 CT/TT genotypes.	Wong, B. S., Camilleri, M., Eckert, D., Carlson, P. and others. (2012). Randomized pharmacodynamic and pharmacogenetic trial of dronabinol effects on colon transit in irritable bowel syndrome-diarrhea. Neurogastroenterol.Motil. 24: 358-e169
Rectal sensitivity	10 IBS patients and 12 healthy volunteers (HV)	Placebo and Δ(9) -THC (5 and 10 mg in healthy volunteers and 10 mg in IBS patients)	The cannabinoid agonist Δ(9) -THC did not alter baseline rectal perception to distension compared to placebo in HV or IBS patients. Similarly, after sigmoid stimulation there were no significant differences between placebo and Δ(9) -THC in sensory thresholds of discomfort.	Klooker, T. K., Leliefeld, K. E., van den Wijngaard, R. M., and Boeckxstaens, G. E. (2011). The cannabinoid receptor agonist delta-9-tetrahydrocannabinol does not affect visceral sensitivity to rectal distension in healthy volunteers and IBS patients. Neurogastroenterol.Motil. 23: 30-5

Crohn's disease (CD)	30 patients (26 males) with CD	Medical cannabis	Of the 30 patients 21 improved significantly after treatment with cannabis. The average Harvey Bradshaw index improved from 14 +/- 6.7 to 7 +/- 4.7 (P < 0.001). The need for other medication was significantly reduced.	Naftali, T., Lev, L. B., Yablecovitch, D., Half, E. and others. (2011). Treatment of Crohn's disease with cannabis: an observational study. Isr.Med.Assoc.J. 13: 455-458
Crohn's disease (CD)	21 patients (mean age, 40 ± 14 y; 13 men)	Twice daily, cigarettes containing 115 mg of Δ9-tetrahydrocannabinol(THC) or placebo containing cannabis flowers from which the THC had been extracted	Complete remission (CDAI score, <150) was achieved by 5 of 11 subjects in the cannabis group (45%) and 1 of 10 in the placebo group (10%; P = .43). A clinical response (decrease in CDAI score of >100) was observed in 10 of 11 subjects in the cannabis group (90%; from 330 ± 105 to 152 ± 109) and 4 of 10 in the placebo group (40%; from 373 ± 94 to 306 ± 143; P = .028).	Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM (2013) Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. Clin Gastroenterol Hepatol. 11(10):1276-1280
Crohn's disease (CD)	21 chronic CD patients	Medical cannabis	Decrease in the CD activity index >100 in 10 of 11 subjects on cannabis compared to 4 of 10 on placebo. Complete remission was achieved in 5 of 11 subjects in the cannabis group and 1 of 10 in the placebo group.	Naftali T, Mechulam R, Lev LB, Konikoff FM. (2014) Cannabis for inflammatory bowel disease. Dig Dis. 32(4):468-74

HIV-1 infection (viral load)	67 patients with HIV-1 infection, 21 days	3.95%-tetrahydrocannabinol marijuana cigarette, a 2.5-mg dronabinol (delta-9-tetrahydrocannabinol) capsule, or a placebo capsule three times daily before meals	The adjusted average changes in viral load in marijuana and dronabinol relative to placebo were -15% (CI, -50% to 34%) and -8% (CI, -37% to 37%), respectively. Neither CD4+ nor CD8+ cell counts appeared to be adversely affected by the cannabinoids.	Abrams, D. I., Hilton, J. F., Leiser, R. J., Shade, S. B. and others. (2003). Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. Ann.Intern.Med. 139: 258-266
ALS	131 respondents (anonymous survey of persons with ALS)	Various (plant derived)	Cannabis may be moderately effective at reducing symptoms of appetite loss, depression, pain, spasticity, and drooling. Cannabis was reported ineffective in reducing difficulties with speech and swallowing, and sexual dysfunction. The longest relief was reported for depression (approximately two to three hours).	Amtmann, D., Weydt, P., Johnson, K. L., Jensen, M. P. and others. (2004). Survey of cannabis use in patients with amyotrophic lateral sclerosis. Am.J.Hosp.Palliat.Care. 21: 95-104
ALS	Open-label crossover 7-month treatment in 20 patients with ALS	Escalating dose study (from 2.5–10 mg) of Marinol	Although the study was not powered sufficiently to detect a statistical significance in primary efficacy variables (FVC, ALSFRS), symptomatic benefits were seen in insomnia, appetite and spasticity.	Gelinas, D. F, Miller, R. G, and Abood, M. (2002). Pilot study of safety and tolerability of delta 9-THC (Marinol) treatment for ALS. Amyotroph Lateral Scler Other Motor Neuron Disord. 3: 23-24.

Cramps in amyotrophic lateral sclerosis	27 ALS patients suffering from moderate to severe (visual analogue scale (VAS); VAS≥4) daily cramps	5 mg THC twice daily followed by placebo or vice versa. Treatment period lasted for 2 weeks and was preceded by a 2-week drug-free observation period (run-in, wash-out period respectively).	THC was well tolerated. There was no evidence for a treatment effect on cramp intensity, number of cramps, fasciculation intensity or any of the other secondary outcome measures.	Weber, M., Goldman, B., and Truniger, S. (2010). Tetrahydrocannabinol (THC) for cramps in amyotrophic lateral sclerosis: a randomised, double-blind crossover trial. J.Neurol.Neurosurg.Psychiatry. 81: 1135-1140.
Dystonia secondary to Wilson's disease	1	Smoked cannabis	A patient with generalized dystonia due to Wilson's disease obtained marked improvement in response to smoking cannabis.	Uribe Roca, M. C., Micheli, F., and Viotti, R. (2005). Cannabis sativa and dystonia secondary to Wilson's disease. Mov Disord. 20: 113-115.
Musician's dystonia	1	THC	General improvement	Jabusch, H. C., Schneider, U., and Altenmuller, E. (2004). Delta9-tetrahydrocannabinol improves motor control in a patient with musician's dystonia. Mov Disord. 19: 990-991.

Dystonic movement disorders	5	Oral doses of CBD rising from 100 to 600 mg/day over a 6 week	Dose-related improvement in dystonia was observed in all patients and ranged from 20 to 50%. Side-effects of CBD were mild and included hypotension, dry mouth, psychomotor slowing, lightheadedness, and sedation.	Consroe, P., Sandyk, R., and Snider, S. R. (1986). Open label evaluation of cannabidiol in dystonic movement disorders. Int.J.Neurosci. 30: 277-282
Generalised and segmental primary dystonia		Nabilone	No significant reduction in dystonia following treatment with nabilone.	Fox, S. H., Kellett, M., Moore, A. P., Crossman, A. R. and others. (2002). Randomised, double-blind, placebo-controlled trial to assess the potential of cannabinoid receptor stimulation in the treatment of dystonia. Mov Disord. 17: 145-149
Psychomotor function	19 male chronic, daily cannabis smokers	Daily cannabis smokers compared to a control group of non-intoxicated occasional drug users	Chronic cannabis smokers' performance on the CTT ($p<0.001$) and the DAT ($p<0.001$) was impaired during baseline relative to the comparison group. Psychomotor performance in the chronic cannabis smokers improved over 3 weeks of abstinence, but did not recover to equivalent control group performance.	Bosker WM, Karschner EL, Lee D, Goodwin RS, Hirvonen J, Innis RB, Theunissen EL, Kuypers KP, Huestis MA, Ramaekers JG (2013) Psychomotor function in chronic daily Cannabis smokers during sustained abstinence. PLoS One. 8(1):e53127

Huntington's Disease (HD)	15 neuroleptic-free patients with Huntington's Disease (HD)	Oral CBD (10 mg/kg/day for 6 weeks) and placebo (sesame oil for 6 weeks)	CBD, at an average daily dose of about 700 mg/day for 6 weeks, was neither symptomatically effective nor toxic, relative to placebo, in neuroleptic-free patients with HD.	Consroe, P., Laguna, J., Allender, J., Snider, S. and others. (1991). Controlled clinical trial of cannabidiol in Huntington's disease. Pharmacol.Biochem.Behav. 40: 701-708.
Huntington's Disease (HD)	44	Nabilone (1 or 2 mg) versus placebo	Nabilone safe and well tolerated, no psychotic episodes. Assessment of either dose of nabilone versus placebo showed a treatment difference of 0.86 (95% CI: -1.8 to 3.52) for total motor score; 1.68 (95% CI: 0.44 to 2.92) for chorea; 3.57 (95% CI: -3.41 to 10.55) for UHDRS cognition; 4.01 (95% CI: -0.11 to 8.13) for UHDRS behavior, and 6.43 (95% CI: 0.2 to 12.66) for the NPI.	Curtis, A., Mitchell, I., Patel, S., Ives, N. and others. (2009). A pilot study using nabilone for symptomatic treatment in Huntington's disease. Mov Disord. 24: 2254-2259.
Huntington's Disease (HD)		Nabilone		Muller-Vahl, K. R., Schneider, U., and Emrich, H. M. (1999). Nabilone increases choreatic movements in Huntington's disease. Mov Disord. 14: 1038-1040.

Huntington's disease (HD)	1	Smoked cannabis and nabilone	The cannabis appeared to improve mood and making patient calmer and more relaxed. Improvements in behavior and reduction of chorea coinciding with the introduction of cannabis and maintained by daily taking nabilone	Curtis, A. and Rickards, H. (2006). Nabilone could treat chorea and irritability in Huntington's disease. J.Neuropsychiatry Clin.Neurosci. 18: 553-554.
Parkinsonian tremor	5	All patients were given on consecutive days: 1) marijuana smoked as a cigarette, 2) diazepam 5 mg orally, 3) levodopa/carbidopa 250 mg/25 mg orally (Sinemet 275), 4) apomorphine 1 5 mg subcutaneously.	None of the patients, including the woman who had previously reported benefit, experienced relief or demonstrated improvement of tremor following marijuana, despite central effects as evidenced by drowsiness or mild euphoria	Frankel, J. P., Hughes, A., Lees, A. J., and Stern, G. M. (1990). Marijuana for parkinsonian tremor. J.Neurol.Neurosurg.Psychiatry. 53: 436.-
Levodopa-induced dyskinesia in PD	7	Nabilone	Nabilone significantly reduces levodopa-induced dyskinesia in PD	Sieradzan, K. A., Fox, S. H., Hill, M., Dick, J. P. and others. (2001). Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: a pilot study. Neurology. 57: 2108-2111

Levodopa-induced dyskinesia in PD	19	A 4-week dose escalation of orally administered cannabis	Cannabis was well tolerated, and had no pro- or antiparkinsonian action. There was no evidence for a treatment effect on levodopa-induced dyskinesia as assessed by the UPDRS, or any of the secondary outcome measures	Carroll, C. B., Bain, P. G., Teare, L., Liu, X. and others. (2004). Cannabis for dyskinesia in Parkinson disease: a randomized double-blind crossover study. Neurology. 63: 1245-1250.
Symptoms of Tourette's syndrome	1	Marijuana	Marijuana appears to have been an effective treatment modality for symptoms of Tourette's syndrome.	Hemming, M. and Yellowlees, P. M. (1993). Effective treatment of Tourette's syndrome with marijuana. Journal of Psychopharmacology. 7: 389-391.
Symptoms of Tourette's syndrome	12 adult TS patients	Single dose of delta9-THC at 5.0 to 10.0 mg	Found no significant differences after treatment with delta9-THC compared to placebo treatment in verbal and visual memory, reaction time, intelligence, sustained attention, divided attention, vigilance, or mood. Only when using the Symptom Checklist 90-R (SCL-90-R) data provide evidence for a deterioration of obsessive-compulsive behavior (OCB) and a trend towards an increase in phobic anxiety	Muller-Vahl, K. R., Koblenz, A., Jobges, M., Kolbe, H. and others. (2001). Influence of treatment of Tourette syndrome with delta9-tetrahydrocannabinol (delta9-THC) on neuropsychological performance. Pharmacopsychiatry. 34: 19-24.

Symptoms of Tourette's syndrome	24 patients with TS	up to 10 mg/day of THC vs placebo	Using the TSSL at 10 treatment days (between days 16 and 41) there was a significant difference ($p < .05$) between both groups. Evidence that THC is effective and safe in the treatment of tics	Muller-Vahl, K. R., Schneider, U., Prevedel, H., Theloe, K. and others. (2003). Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. J.Clin.Psychiatry. 64: 459-465.
Symptoms of Tourette's syndrome	12 adult TS patients	Single-dose trial of Delta(9)-THC (5.0, 7.5 or 10.0 mg)	Using the TSSL, there was a significant improvement of tics ($p=0.015$) and obsessive-compulsive behavior (OCB) ($p = 0.041$) after treatment with Delta(9)-THC compared to placebo. Examiner ratings demonstrated a significant difference for the subscore "complex motor tics" ($p = 0.015$) and a trend towards a significant improvement for the subscores "motor tics" ($p = 0.065$), "simple motor tics" ($p = 0.093$), and "vocal tics" ($p = 0.093$). No serious adverse reactions occurred.	Müller-Vahl KR, Schneider U, Koblenz A, Jöbges M, Kolbe H, Daldrup T, Emrich HM. Treatment of Tourette's syndrome with Delta 9-tetrahydrocannabinol (THC): a randomized crossover trial. Pharmacopsychiatry. 2002 Mar;35(2):57-61

Sleep in fibromyalgia		Nabilone		Ware M, FitzcharlesMA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Paper presented at: Canadian Rheumatology Association Meeting; February 18-21, 2009; Kananaskis, AB: Canada. Abstract 149 J Rheumatol. 2009;36(11):2607
Symptoms of Tourette's syndrome	24 patients suffering from TS	10 mg Delta(9)-THC over a 6-week period	Measuring immediate verbal memory span, we even found a trend towards a significant improvement during and after treatment. Results from this study corroborate previous data suggesting that in patients suffering from TS, treatment with Delta(9)-THC causes neither acute nor long-term cognitive deficits.	Müller-Vahl KR, Prevedel H, Theloe K, Kolbe H, Emrich HM, Schneider U. Treatment of Tourette syndrome with delta-9-tetrahydrocannabinol (delta 9-THC): no influence on neuropsychological performance. Neuropsychopharmacology. 2003 Feb;28(2):384-8.
Symptoms of Tourette's syndrome	28	Delta-9-Tetrahydrocannabinol (Delta(9)THC), either as monotherapy or as adjuvant therapy, with placebo	Positive effect from Delta(9)THC, the improvements in tic frequency and severity were small and were only detected by some of the outcome measures	Curtis, A., Clarke, C. E., and Rickards, H. E. (2009). Cannabinoids for Tourette's Syndrome. Cochrane.Database.Syst.Rev. CD006565.-

Sleep in fibromyalgia		Nabilone		Fitzcharles MA, Shir Y, Joseph L, Ware MA. (2009) The effects of nabilone on insomnia in fibromyalgia: results of a randomized controlled trial. Paper presented at: American College of Rheumatology/ Association of Rheumatology Health Professionals Annual Scientific Meeting (ACR/ARHP 09); November 6-11, 2009; Atlanta: GA. Arthritis Rheum. 60:1429.
Sleep in fibromyalgia		Nabilone 0.5-1mg vs amitriptyline 10-20mg		McGill University Health Center. Nabilone versus amitriptyline in improving quality of sleep in patients with fibromyalgia. ClinicalTrials.gov. http: //ClinicalTrials.gov/show/NCT00 381199 Accessed April 7, 2014.

Sleep disturbance in fibromyalgia (FM)	29	Nabilone (0.5-1.0 mg before bedtime) vs amitriptyline (10-20 mg before bedtime)	Although sleep was improved by both amitriptyline and nabilone, nabilone was superior to amitriptyline (Insomnia Severity Index difference = 3.2; 95% confidence interval = 1.2-5.3). Nabilone was marginally better on the restfulness (Leeds Sleep Evaluation Questionnaire difference = 0.5 [0.0-1.0]) but not on wakefulness (difference = 0.3 [-0.2 to 0.8]). No effects on pain, mood, or quality of life were observed. AEs were mostly mild to moderate and were more frequent with nabilone.	Ware, M. A., Fitzcharles, M. A., Joseph, L., and Shir, Y. (2010). The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesth.Analg. 110: 604-610.
Sleep disturbance	17 heavy MJ users discontinuing MJ use and 14 drug-free controls. Men and women were studied, 18 to 30 years.	Cannabis	The MJ users showed differences in PSG measures (lower total sleep times, and less slow wave sleep than the control group) on both nights; they also showed worse sleep efficiency, longer sleep onset, and shorter REM latency than the control group on Night 2. More sleep continuity parameters were significantly worse for the MJ group than the control group on Night 2 versus Night 1, indicating that sleep in the MJ group was relatively worse on Night 2 compared to Night 1.	Bolla, K. I., Lesage, S. R., Gamaldo, C. E., Neubauer, D. N. and others. (2008). Sleep disturbance in heavy marijuana users. Sleep. 31: 901-908.

Sleep disturbance	18 heavy MJ users	Cannabis	Across abstinence, Total Sleep Time (TST), Sleep Efficiency (SEff), and amount of REM sleep declined, while Wake after Sleep Onset (WASO) and Periodic Limb Movements (PLM) increased. Furthermore, quantity (joints/week) and duration (years) of MJ use were positively associated with more PLMs.	Bolla, K. I., Lesage, S. R., Gamaldo, C. E., Neubauer, D. N. and others. (2010). Polysomnogram changes in marijuana users who report sleep disturbances during prior abstinence. Sleep Med. 11: 882-889.
Obstructive Sleep Apnea (OSA)	17 adults with a baseline Apnea Hypopnea Index (AHI) ≥15/h	Dronabinol starting at 2.5 mg once daily. The dose was increased weekly, as tolerated, to 5 mg and finally to 10 mg once daily	Dronabinol treatment is safe and well-tolerated in OSA patients at doses of 2.5-10 mg daily and significantly reduces AHI in the short-term.	Prasad B, Radulovacki MG, Carley DW. (2013) Proof of concept trial of dronabinol in obstructive sleep apnea. Front Psychiatry. 22;4:1
Somnolence in chronic daily cannabis smokers	13 male chronic daily cannabis smokers	THC doses (20 mg) around-the-clock for 7 days (40-120 mg daily)	Higher evening THC and 11-OH-THC concentrations were significantly associated with shorter sleep latency, less difficulty falling asleep, and more daytime sleep the following day. In contrast, the duration of calculated and self-reported nighttime sleep decreased slightly (3.54 and 5.34 minutes per night, respectively) but significantly during the study.	Gorelick DA1, Goodwin RS, Schwilke E, Schroeder JR, Schwope DM, Kelly DL, Ortemann-Renon C, Bonnet D, Huestis MA. (2013) Around-the-clock oral THC effects on sleep in male chronic daily cannabis smokers. Am J Addict. 22(5):510-4

Intraocular pressure (IOP)	6 patients with ocular hypertension or early primary open angle glaucoma	Sublingual dose of 5 mg Delta-9-THC, 20 mg CBD, 40 mg CBD, or placebo	Two hours after sublingual administration of 5 mg Delta-9-THC, the IOP was significantly lower than after placebo (23.5 mm Hg vs. 27.3 mm Hg, P=0.026). The IOP returned to baseline level after the 4-hour IOP measurement. CBD administration did not reduce the IOP at any time.	Tomida, I., Azuara-Blanco, A., House, H., Flint, M. and others. (2006). Effect of sublingual application of cannabinoids on intraocular pressure: a pilot study. J.Glaucoma. 15: 349-353.
Intraocular pressure (IOP)	8	WIN 55212--2, applied topically at doses of 25 or 50 microg	Decreases the intraocular pressure of human glaucoma resistant to conventional therapies within the first 30 min (15 +/- 0.5% and 23 +/- 0.9%). A maximal reduction of 20 +/- 0.7% and 31 +/- 0.6% is reached in the first 60 min.	Porcella, A., Maxia, C., Gessa, G. L., and Pani, L. (2001). The synthetic cannabinoid WIN55212-2 decreases the intraocular pressure in human glaucoma resistant to conventional therapies. Eur.J.Neurosci. 13: 409-412.
Intraocular pressure (IOP)	1	Marijuana, Marinol	Dramatic effect (lowering).	Zhan, G. L., Camras, C. B., Palmberg, P. F., and Toris, C. B. (2005). Effects of marijuana on aqueous humor dynamics in a glaucoma patient. J.Glaucoma. 14: 175-177

Arterial and intraocular hypertension	Systemic normotensive (N=8) and hypertensive (N=8) open-angle glaucoma patients (N=16)	Inhalation of tetrahydrocannabinol (THC) (2.8%)	The salient observation after THC inhalation was that the changes in ocular pressure paralleled the changes in blood pressure in each glaucoma patient. These findings suggest that the positive chronotropic response to THC tends to maintain cardiac output which limits further decreases in blood pressure and the capillary filtration of aqueous humor decreases or the reabsorption of aqueous humor increases because of the systemic hypotensive effect attending THC inhalation.	Crawford, W. J. and Merritt, J. C. (1979).Effects of tetrahydrocannabinol on arterial and intraocular hypertension. Int.J.Clin.Pharmacol.Biopharm. 17: 191-196.
Histamine-evoked somatosensory and vascular responses	12 (Study 1, iontophoresis) and six participants (Study 2, microdialysis)	HU210 (cannabinoid receptor agonist) by skin patch (50 mM) or dermal microdialysis (5 mM)	In humans peripheral administration of a cannabinoid receptor agonist attenuates histamine-induced itch. The observation that protein extravasation was not decreased demonstrates that the alleviation of itch is not due to an anti-histaminergic property of HU210. The reduced neurogenic flare reaction indicates an attenuated antidromic nerve fibre activation and neuropeptide release.	Dvorak, M., Watkinson, A., McGlone, F., and Rukwied, R. (2003). Histamine induced responses are attenuated by a cannabinoid receptor agonist in human skin. Inflamm.Res. 52: 238-245.

Regional cerebral blood flow	10 healthy male volunteers	Oral dose of CBD (400 mg) or placebo	CBD significantly decreased subjective anxiety and increased mental sedation, while placebo did not induce significant changes. Assessment of brain regions where anxiolyticeffects of CBD were predicted a priori revealed two voxel clusters of significantly decreased ECD uptake in the CBD relative to the placebo condition ($p<0.001$, uncorrected for multiple comparisons).	Crippa, J. A., Zuardi, A. W., Garrido, G. E., Wichert-Ana, L. and others. (2004). Effects of cannabidiol (CBD) on regional cerebral blood flow. Neuropsychopharmacology. 29: 417-426
End-stage open-angle glaucoma	9	Either orally administered delta-9-tetrahydrocannabinol capsules or inhaled marijuana in addition to their existing therapeutic regimen	An initial decrease in intraocular pressure was observed in all patients, and the investigator's therapeutic goal was met in four of the nine patients. However, the decreases in intraocular pressure were not sustained, and all patients elected to discontinuetreatment within 1 to 9 months for various reasons.	Flach, A. J. (2002). Delta-9-tetrahydrocannabinol (THC) in the treatment of end-stage open-angle glaucoma. Trans.Am.Ophthalmol.Soc. 100: 215-222

Heterogenous glaucomas	18	Marihuana inhalation	The hypotensive effects appeared in 60 to 90 minutes as the decrease in intraocular pressure(IOP) appeared to follow the decrease in blood pressure. In addition to any local effect, the mechanism of lowered to any localeffect, the mechanism of lowered IOP may also involve the decreased pressure perfusing the ciliary body vasculature as a result of the peripheral vasodilatory properties of marihuana.	Merritt, J. C., Crawford, W. J., Alexander, P. C., Anduze, A. L. and others. (1980). Effect of marihuana on intraocular and blood pressure in glaucoma. Ophthalmology. 87: 222-228.
Specific airway conductance (Gaw/VL) and the maximal expiratory flow	6 control and six asthmaticsubjects	10 mg of delta9-tetrahydrocannabinol	In control subjects, there was a slight but statistically significant increase in Gaw/VL after oral administration of delta9-tetrahydrocannabinol; however, there was no significant increase in Vmax 50%. One of the asthmatic patients developed severe bronchoconstriction following administration of delta9-tetrahydrocannabinol; among the remaining five patients, there were variable changes in Gaw/VL and Vmax 50% after oral administration of delta9-tetrahydrocannabinol, but mean changes were not significant.	Abboud, R. T. and Sanders, H. D. (1976). Effect of oral administration of delta-tetrahydrocannabinol on airway mechanics in normal and asthmatic subjects. Chest. 70: 480-485

Bronchial dynamics and respiratory-center sensitivity	17 normal volunteers with previous marihuana smoking experience	3.23 mg per kilogram of marihuana, using a bag-in-box technic	Marihuana smoke, unlike cigarette smoke, causes bronchodilatation rather than bronchoconstriction and, unlike opiates, does not cause central respiratory depression.	Vachon, L., FitzGerald, M. X., Solliday, N. H., Gould, I. A. and others. (1973). Single-dose effects of marihuana smoke. Bronchial dynamics and respiratory-center sensitivity in normal subjects. N.Engl.J.Med. 288: 985-989.
Acute pulmonary physiologic effects	32 healthy, experienced male marijuana smokers	1 or 2 per cent Δ9-tetrahydrocannabinol (smoking) or ingestion of 10, 15 and 20 mg of Δ9-tetrahydrocannabinol	Both smoked marijuana and oral Δ9-tetrahydrocannabinol cause definite dilatation of the airways lasting as long as 60 minutes and six hours, respectively.	Tashkin, D. P., Shapiro, B. J., and Frank, I. M. (1973). Acute pulmonary physiologic effects of smoked marijuana and oral 9 -tetrahydrocannabinol in healthy young men. N.Engl.J.Med. 289: 336-341
Plethysmographically determined airway resistance (Raw) and specific airway conductance (SGaw)	10 subjects with stable bronchial asthma	2 per cent natural marijuana (7 mg per kg) and 15 mg of oral Delta-9-tetrahydrocannabinol (THC) vs placebo	After smoked marijuana, SGaw increased immediately and remained significantly elevated (33 to 48 per cent above initial control values) for at least 2 hours, whereas SGaw did not change after placebo. After ingestion of 15 mg of THC, SGaw was elevated significantly at 1 and 2 hours, and Raw was reduced significantly at 1 to 4 hours, whereas no changes were noted after placebo.	Tashkin, D. P., Shapiro, B. J., and Frank, I. M. (1974). Acute effects of smoked marijuana and oral delta9-tetrahydrocannabinol on specific airway conductance in asthmatic subjects. Am.Rev.Respir.Dis. 109: 420-428.

Experimental induction of acute bronchospasm	8 subjects with clinically stable bronchial asthma	500 mg of smoked marijuana (2.0 per cent delta9-tetrahydrocannabinol) compared with those of 500 mg of smoked placebo marijuana (0.0 per cent delta9-tetrahydrocannabinol), 0.25 ml of aerosolized saline, and 0.25 ml of aerosolized isoproterenol (1,250 mug)	After methacholine-inducedbronchospasm, placebo marijuana and saline inhalation produced minimal changes in specific airway conductance and thoracic gas volume, whereas 2.0 per cent marijuana and isoproterenol each caused a prompt correction of the bronchospasm and associated hyperinflation	Tashkin, D. P., Shapiro, B. J., Lee, Y. E., and Harper, C. E. (1975). Effects of smoked marijuana in experimentally induced asthma. Am.Rev.Respir.Dis. 112: 377-

Bronchodilation		Delta 8-tetrahydrocannabinol (delta 8-THC), cannabinol (CBN), and cannabidiol (CBD) in maximal doses of 75 mg, 1200 mg, and 1200 mg, delta 8-THC (75 mg), delta 9-tetrahydrocannabinol (delta 9-THC), combinations of CBN and CBD with delta 9-THC (5 mg)	Delta 9-THC and, to a lesser extent, delta 8-THC, have acute bronchodilator activity but that CBN, CBD, and their combinations do not provide effective bronchodilation. The daily use of delta 9-THC was not associated with clinical tolerance.	Gong, H., Jr., Tashkin, D. P., Simmons, M. S., Calvarese, B. and others. (1984). Acute and subacute bronchial effects of oral cannabinoids. Clin.Pharmacol.Ther. 35: 26-32.
Bronchodilation	10 volunteer inpatient asthmatics in a steady state	Placebo-ethanol only; delta1-tetrahydrocannabinol (THC) 200 mug in ethanol; or salbutamol 100 mug (Ventolin inhaler)	Salbutamol and THC significantly improved ventilatory function. Maximal bronchodilatation was achieved more rapidly with salbutamol, but at 1 hour both drugs were equally effective. No cardiovascular or mood disturbance was detected, and plasma total cannabinoids at 15 minutes were undectable by radioimmunoassay.	Williams, S. J., Hartley, J. P., and Graham, J. D. (1976). Bronchodilator effect of delta1-tetrahydrocannabinol administered by aerosol of asthmatic patients. Thorax. 31: 720-723.

Bronchodilation		Delta1-trans-tetrahydrocannabinol, (delta1-THC)	It increased peak expiratory flow rate (PEFR) and forced expiratory volume in 1 second (FEV1). The rate of onset, magnitude, and duration of the bronchodilator effect was dose related.	Hartley, J. P., Nogrady, S. G., and Seaton, A. (1978). Bronchodilator effect of delta1-tetrahydrocannabinol. Br.J.Clin.Pharmacol. 5: 523-525.
Bronchodilation	16 patients with proven reversible airways obstruction	Oral delta-1-(trans)-tetrahydrocannabinol (delta-1-THC) and salbutamol	Measurements of forced vital capacity, forced expired volume in one second, peak expiratory flow rate, and maximum expiratory flow rate at 50 percent vital capacity after 10 mg oral delta-1-THC did not differ significantly from the effect of placebo, whereas increases after salbutamol were significant.	Davies, B. H., Radcliffe, S., Seaton, A., and Graham, J. D. (1975). A trial of oral delta-1-(trans)-tetrahydrocannabinol in reversible airways obstruction. Thorax. 30: 80-85.
Bronchomotor effect	6 healthy and six asthmatic subjects	Oral nabilone (2 mg)	Bronchodilation following nabilone was intermediate between that of terbutalineand placebo in the healthy subjects but was equivalent to placebo in the asthmatics.	Gong, H., Jr., Tashkin, D. P., and Calvarese, B. (1983). Comparison of bronchial effects of nabilone and terbutaline in healthy and asthmatic subjects. J.Clin.Pharmacol. 23: 127-133.

Subacute effects of heavy marihuana smoking on the lung	28 healthy young male experienced cannabis users	Before and after 47 to 59 days of daily ad-libitum marihuana smoking (mean of 5.2 marihuana cigarettes per day per subject, 2.2 per cent delta9-tetrahydrocannabinol)	After 47 to 59 days of heavy smoking, statistically significant decreases in forced expired volume in one second (3 +/- 1 per cent, S.E.), maximal mid-expiratory flow rate (11 +/- 2 per cent), plethysmographic specific airway conductance (16 +/- 2 per cent) and diffusing capacity (8 +/- 2 per cent) were noted as compared with the base-line studies.	Tashkin, D. P., Shapiro, B. J., Lee, Y. E., and Harper, C. E. (1976). Subacute effects of heavy marihuana smoking on pulmonary function in healthy men. N.Engl.J.Med. 294: 125-129.
Cognitive function in patients with multiple sclerosis	Two groups, each of 25 patients with MS (cannabis users and nonusers)	Cannabis	Cannabis users performed significantly more poorly than nonusers on measures of information processing speed, working memory, executive functions, and visuospatial perception. They were also twice as likely as nonusers to be classified as globally cognitively impaired. There were no between-group differences on the HADS measures of depression and anxiety or lifetime SCID-I psychiatric diagnoses.	Honarmand, K., Tierney, M. C., O'Connor, P., and Feinstein, A. (2011). Effects of cannabis on cognitive function in patients with multiple sclerosis. Neurology. 76: 1153-1160.

Cognitive function in patients with multiple sclerosis	17 cannabis-naïve patientswith MS were assessed at baseline and at the end of the cannabis and placebo phases of the trial	Free-dose cannabis plant extract (Sativex)	Cannabinoid treatment did not induce psychopathology and did not impair cognition in cannabis-naïve patientswith MS. However, the positive correlation between blood levels of Delta-9-tetrahydrocannabinol and psychopathological scores suggests that at dosages higher than those used in therapeutic settings, interpersonal sensitivity, aggressiveness, and paranoiac features might arise.	Aragona M, Onesti E, Tomassini V, Conte A, Gupta S, Gilio F, Pantano P, Pozzilli C, Inghilleri M. (2009). Psychopathological and cognitive effects of therapeutic cannabinoids in multiple sclerosis: a double-blind, placebo controlled, crossover study. Clin Neuropharmacol. Jan-Feb;32(1):41-7
Cognitive function in patients with multiple sclerosis	20 subjects with MS who smoked cannabis and 19 noncannabis users with MS	Cannabis	The cannabis group performed more poorly on the more demanding of the Paced Auditory Serial Addition Test tasks (i.e., 2-second version) ($p < 0.02$) and the 10/36 Spatial Recall Test ($p < 0.03$). Cannabis users had more diffuse cerebral activation across all N-Back trials and made more errors on the 2-Back task ($p < 0.006$), during which they displayed increased activation relative to nonusers in parietal ($p < 0.007$) and anterior cingulate ($p < 0.001$) regions implicated in working memory.	Pavisian B, MacIntosh BJ, Szilagyi G, Staines RW, O'Connor P, Feinstein A2. (2014) Effects of cannabis on cognition in patients with MS: a psychometric and MRI study. Neurology. 2014 May 27;82(21):1879-87

Depression	4400 adult internet users	Marijuana daily, once a week or less, or never	Daily users reported less depressed mood and more positive affect than non-users. The three groups did not differ on interpersonal symptoms. Separate analyses for medical vs. recreational users demonstrated that medical usersreported more depressed mood and more somatic complaints than recreational users, suggesting that medical conditions clearly contribute to depression scores and should be considered in studies of marijuana and depression.	Denson, T. F. and Earleywine, M. (2006). Decreased depression in marijuana users. Addict.Behav. 31: 738-742.
Generalized social anxiety disorder (SAD)	10 treatment-naïve patients with SAD	Oral dose of CBD (400 mg) or placebo	Relative to placebo, CBD was associated with significantly decreased subjective anxiety ($p < 0.001$), reduced ECD uptake in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus ($p < 0.001$, uncorrected), and increased ECD uptake in the right posterior cingulate gyrus ($p < 0.001$, uncorrected).	Crippa JA, Derenusson GN, Ferrari TB, Wichert-Ana L, Duran FL, Martin-Santos R, Simões MV, Bhattacharyya S, Fusar-Poli P, Atakan Z,Santos Filho A, Freitas-Ferrari MC, McGuire PK, Zuardi AW, Busatto GF, Hallak JE. (2011) Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. J Psychopharmacol. 2011 Jan;25(1):121-30

Generalized social anxiety disorder (SAD)	24 never-treated patients with SAD	CBD (600 mg; n=12) or placebo (placebo; n=12)	Pretreatment with CBD significantly reduced anxiety, cognitive impairment and discomfort in their speech performance, and significantly decreased alert in their anticipatory speech. The placebo group presented higher anxiety, cognitive impairment, discomfort, and alert levels when compared with the control group as assessed with the VAMS.	Bergamaschi, M. M., Queiroz, R. H., Chagas, M. H., de Oliveira, D. C. and others. (2011). Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. Neuropsychopharmacology. 36: 1219-1226
Driving behavior	24 experienced driver participants	Dronabinol (Marinol®; 10 and 20 mg) and placebo	Treatment effects of dronabinol on weaving were comparable with driving on the road but inter-individual variability seemed higher in the simulator than on the road which may have potential effects on the clinical inferences made from simulator driving.	Veldstra JL, Bosker WM, de Waard D, Ramaekers JG, Brookhuis KA. (2015) Comparing treatment effects of oral THC on simulated and on-the-road driving performance: testing the validity of driving simulator drug research. Psychopharmacology (Berl). 232(16):2911-9

THC induced anxiety		0.5 mg/kg delta 9-THC, 1 mg/kg CBD, a mixture containing 0.5 mg/kg delta 9-THC and 1 mg/kg CBD and placebo and diazepam (10 mg)	CBD blocks the anxiety provoked by delta 9-THC, however this effect also extended to marihuana-like effects and to other subjective alterations induced by delta 9-THC. This antagonism does not appear to be caused by a general block of delta 9-THC effects, since no change was detected in the pulse-rate measurements. Several further effects were observed typical of CBD and of an opposite nature to those of delta 9-THC.	Zuardi, A. W., Shirakawa, I., Finkelfarb, E., and Karniol, I. G. (1982). Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. Psychopharmacology (Berl). 76: 245-250
Anxiety	15 healthy men who had used cannabis 15 times or less in their life	10 mg of Delta9-THC, 600 mg of CBD, or a placebo	Delta9-Tetrahydrocannabinol increased anxiety, as well as levels of intoxication, sedation, and psychotic symptoms, whereas there was a trend for a reduction in anxiety following administration of CBD.	Fusar-Poli, P., Crippa, J. A., Bhattacharyya, S., Borgwardt, S. J. and others. (2009). Distinct effects of (26)9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. Arch.Gen.Psychiatry. 66: 95-105.

Paranoia	121 individuals with paranoid ideation	Placebo, THC, or THC preceded by a cognitive awareness condition	THC significantly increased paranoia, negative affect (anxiety, worry, depression, negative thoughts about the self), and a range of anomalous experiences, and reduced working memory capacity. The increase in negative affect and in anomalous experiences fully accounted for the increase in paranoia. Working memory changes did not lead to paranoia.	Freeman D, Dunn G, Murray RM, Evans N, Lister R, Antley A, Slater M, Godlewska B, Cornish R, Williams J, Di Simplicio M,Igoumenou A, Brenneisen R, Tunbridge EM, Harrison PJ, Harmer CJ, Cowen P, Morrison PD (2015) How cannabis causes paranoia: using the intravenous administration of Δ9-tetrahydrocannabinol(THC) to identify key cognitive mechanisms leading to paranoia. Schizophr Bull. 41(2):391-9
Psychotic symptoms induced by Delta-9-tetrahydrocannabinol	15 healthy men with minimal earlier exposure to cannabis	Delta-9-tetrahydrocannabinol (Delta-9-THC) and Cannabidiol (CBD)	Delta-9-THC and CBD had opposite effects on activation relative to placebo in the striatum during verbal recall, in the hippocampus during the response inhibition task, in the amygdala when subjects viewed fearful faces, in the superior temporal cortex when subjects listened to speech, and in the occipital cortex during visual processing. Delta-9-THC and CBD can have opposite effects on regional brain function, which may underlie their different symptomatic and behavioral effects, and CBD's ability to block the psychotogenic effects of Delta-9-THC.	Bhattacharyya, S., Morrison, P. D., Fusar-Poli, P., Martin-Santos, R. and others. (2010). Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology. 35: 764-774.

Posttraumatic stress disorder (PTSD)	47 patients diagnosed with PTSD and having continuing nightmares in spite of conventional antidepressants and hypnotics	Nabilone	The majority of patients (72%) receiving nabilone experienced either cessation of nightmares or a significant reduction in nightmare intensity. Subjective improvement in sleep time, the quality of sleep, and the reduction of daytime flashbacks and nightsweats were also noted by some patients.	Fraser, G. A. (2009). The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in posttraumatic stress disorder (PTSD). CNS.Neurosci.Ther. 15: 84-88
Posttraumatic stress disorder (PTSD)	Canadian male military personnel with PTSD	Nabilone capsules (NAB) 0.5mg to maximum of 3.0mg or placebo (PBO)	NAB provided significant relief for military personnel with PTSD, The mean reduction in nightmares as measured by the CAPS Recurring and Distressing Dream scores were -3.6 ± 2.4 and -1.0 ± 2.1 in the NAB and PBO groups, respectively (p=0.03).	Jetly R, Heber A, Fraser G, Boisvert D (2015) The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study. Psychoneuroendocrinology. 51:585-8
PTSD	104 male inmates with serious mental illness	Nabilone 4.0 mg	Results indicated significant improvement in PTSD-associated insomnia, nightmares, PTSD symptoms, and Global Assessment of Functioning and subjective improvement in chronic pain. There was no evidence of abuse within this high-risk population or reduction of efficacy when nabilone was given in powder form with water rather than as a capsule.	Cameron C, Watson D, Robinson J (2015) Use of a synthetic cannabinoid in a correctional population for posttraumatic stress disorder-related insomnia and nightmares, chronic pain, harm reduction, and other indications: a retrospective evaluation. J ClinPsychopharmacol. 34(5):559-64

Nighttime agitation in patients with dementia	6 consecutive patients in the late stages of dementia and suffering from circadian and behavioral disturbances-five patients with Alzheimer's disease and one patient with vascular dementia	2.5 mg dronabinol daily for 2 weeks	Compared to baseline, dronabinol led to a reduction in nocturnal motor activity (P=0.028). These findings were corroborated by improvements in Neuropsychiatric Inventory total score (P=0.027) as well as in subscores for agitation, aberrant motor, and nighttime behaviors (P<0.05). No side effects were observed.	Walther, S., Mahlberg, R., Eichmann, U., and Kunz, D. (2006). Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. Psychopharmacology (Berl). 185: 524-528.
Dementia-related agitation	1	Nabilone (initially 0.5 mg at bedtime, and then twice per day)	Immediate reduction in the severity of agitation and resistiveness and eventual improvement in various behavioural symptoms following six weeks of continuous treatment	Passmore, M. J. (2008). The cannabinoid receptor agonist nabilone for the treatment of dementia-related agitation. Int.J.Geriatr.Psychiatry. 23: 116-117.

Agitation and aggressive behavior in severely demented patients	40 inpatients	Dronabinol	The addition of dronabinol to patients' treatment regimens was associated with significant decreases in all domains of the Pittsburgh Agitation Scale. There were also significant improvements in Clinical Global Impression scores, sleep duration and percentage of meals consumed during the treatment periods. Twenty-six adverse events were recorded during dronabinoltreatment, none of which led to medication discontinuation.	Woodward MR, Harper DG2, Ellison JM2. (2014) Dronabinol for the treatment of agitation and aggressive behavior in acutely hospitalized severely demented patients with noncognitive behavioral symptoms. Am J Geriatr Psychiatry. 22(4):415-9
Dementia-related neuropsychiatric symptoms (NPS)	24 patients received THC and 26 received placebo	THC 1.5 mg or matched placebo (1:1) 3 times daily for 3 weeks	This study provides Class I evidence that for patients with dementia-related NPS, low-dose THC does not significantly reduce NPS at 21 days, though it is well-tolerated.	van den Elsen GA, Ahmed AI, Verkes RJ, Kramers C, Feuth T, Rosenberg PB, van der Marck MA, Olde Rikkert MG (2015). Tetrahydrocannabinol for neuropsychiatric symptoms in dementia: A randomized controlled trial. Neurology. 9;84(23):2338-46

Emotional processing	48 volunteers	THC (8mg), CBD (16mg), THC+CBD (8mg+16mg) and placebo, by inhalation	In comparison to placebo, CBD improved emotional facial affect recognition at 60% emotional intensity; THC was detrimental to the recognition of ambiguous faces of 40% intensity. The combination of THC+CBD produced no impairment. Relative to placebo, both THC alone and combined THC+CBD equally increased feelings of being 'stoned'. CBD did not influence feelings of 'stoned'.	Hindocha C1, Freeman TP2, Schafer G2, Gardener C2, Das RK2, Morgan CJ3, Curran HV (2015) Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: a randomised, double-blind, placebo-controlled study in cannabis users. Eur Neuropsychopharmacol. 2015 Mar;25(3):325-34
Progressive Inflammatory brain Disease (CUPID)	Patients were randomised in a 2 : 1 ratio to Δ(9)-THC or placebo; Adults aged 18-65 years with primary or secondary progressive MS (493 (329 active and 164 placebo))	Oral Δ(9)-THC (maximum 28 mg/day) or matching placebo; Visits - Three and 6 months, and then 6-monthly up to 36 or 42 months.	The CUPID trial failed to demonstrate a significant treatment effect in primary or secondary outcomes. There were no major safety concerns, but unwanted side effects seemed to affect compliance. The intervention had significant additional costs with no improvement in health outcomes; therefore, it was dominated by usual care and not cost-effective.	Ball S, Vickery J, Hobart J, Wright D, Green C, Shearer J, Nunn A, Cano MG, MacManus D, Miller D, Mallik S, Zajicek J (2015) The Cannabinoid Use in Progressive Inflammatory brain Disease (CUPID) trial: a randomised double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of cannabinoids to slow progression in multiple sclerosis. Health Technol Assess. 2015 Feb;19(12):vii-viii, xxv-xxxi, 1-187.

Antitumoral action	9 patients with recurrent glioblastoma multiforme	THC intratumoraly	Cannabinoid delivery was safe and could be achieved without overt psychoactive effects. Median survival of the cohort from the beginning of cannabinoid administration was 24 weeks (95% confidence interval: 15-33). Delta(9)-Tetrahydrocannabinol inhibited tumour-cell proliferation in vitro and decreased tumour-cell Ki67 immunostaining when administered to two patients.	Guzman, M., Duarte, M. J., Blazquez, C., Ravina, J. and others. (2006). A pilot clinical study of Delta9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. Br.J.Cancer. 95: 197-203.
Olfaction	15 subjects	20 mg oral THC	Olfactory thresholds were increased and odour discrimination performance was reduced.	Walter C, Oertel BG, Ludyga D, Ultsch A, Hummel T, Lötsch J. (2014) Effects of 20 mg oral Δ(9) - tetrahydrocannabinol on the olfactory function of healthy volunteers. Br J Clin Pharmacol. 78(5):961-9

Management of cannabis withdrawal	A volunteer sample of 49 dependent cannabis users	Cannabis	Cannabis Withdrawal Scale has excellent psychometric properties. Nightmares and/or strange dreams was the most valid item (Wald χ^2=105.6, P<0.0001), but caused relatively little associated distress (Wald χ^2=25.11, P=0.03). Angry outbursts were considered intense (Wald χ^2=73.69, P<0.0001) and caused much associated distress (Wald χ^2=45.54, P<0.0001). Trouble getting to sleep was also an intense withdrawal symptom (Wald χ^2=42.31, P<0.0001) and caused significant associated distress (Wald χ^2=47.76, P<0.0001).	Allsop, D. J., Norberg, M. M., Copeland, J., Fu, S. and others. (2011). The Cannabis Withdrawal Scale development: patterns and predictors of cannabis withdrawal and distress. Drug Alcohol Depend. 119: 123-129
Cannabis dependence or withdrawal	51 DSM-IV-TR cannabis-dependent treatment seekers	86.4 mg of Δ9-tetrahydrocannabinol and 80 mg of cannabidiol) (Sativex) or placebo	Nabiximols treatment significantly reduced the overall severity of cannabis withdrawal relative to placebo (F8,377.97 = 2.39; P = .01), including effects on withdrawal-related irritability, depression, and cannabis cravings. Nabiximols had a more limited, but still positive, therapeutic benefit on sleep disturbance, anxiety, appetite loss, physical symptoms, and restlessness.	Allsop DJ, Copeland J, Lintzeris N, Dunlop AJ, Montebello M, Sadler C, Rivas GR, Holland RM, Muhleisen P, Norberg MM,Booth J, McGregor IS. (2014) Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. JAMA Psychiatry. 71(3):281-91

Cannabis dependence or withdrawal	7 cannabis users	Ascending order in 15 mg increments across separate sessions, up to a maximum of 90 mg oral THC	Considerable variability in Cmax and tmax was observed. Doses of oral Δ(9) -THC larger than those tested previously can be administered to individuals with a history of cannabis use, although given the pharmacokinetic variability of oral Δ(9) -THC and individual differences in sensitivity, individualized dose adjustment is needed to avoid side effects and maximize therapeutic response.	Lile JA, Kelly TH, Charnigo RJ, Stinchcomb AL, Hays LR (2013) Pharmacokinetic and pharmacodynamic profile of supratherapeutic oral doses of Δ(9) -THC in cannabis users. J Clin Pharmacol. 53(7):680-90
Cannabis dependence or withdrawal	One 20-year-old woman who developed protracted nausea and vomiting secondary to cannabis withdrawal	Nabilone	The patient was successfully treated with nabilone.	Lam PW, Frost DW (2015) Nabilone therapy for cannabis withdrawal presenting as protracted nausea and vomiting. BMJ Case Rep. 2014 Sep 22; 2014

Cannabis dependence or withdrawal	Nontreatment-seeking marijuana smokers (8 men and 3 women)	Nabilone, different dose (0, 6, 8 mg/day)	Both nabilone dose conditions decreased marijuana relapse and reversed withdrawal-related irritability and disruptions in sleep and food intake ($p<0.05$). Nabilone (8 mg/day) modestly worsened psychomotor task performance. Neither dose condition increased ratings of capsule 'liking' or desire to take the capsules relative to placebo.	Haney M, Cooper ZD, Bedi G, Vosburg SK, Comer SD, Foltin RW (2013) Nabilone decreases marijuana withdrawal and a laboratory measure of marijuana relapse. Neuropsychopharmacology. 38(8):1557-65
Dronabinol Treatment for Marijuana Addiction	156	Dronabinol: 20mg bid for a daily maximum dose of 40mg vs Placebo	Although both groups showed a reduction in marijuana use over time, there were no differences between the groups. Treatment retention was significantly higher at the end of the maintenance phase on dronabinol (77%), compared to placebo (61%) (P=.02), and withdrawal symptoms were significantly lower on dronabinol than placebo (P=.02).	Levin FR, Mariani JJ, Brooks DJ, Pavlicova M, Cheng W, Nunes EV (2011) Dronabinol for the treatment of cannabis dependence: a randomized, double-blind, placebo-controlled trial Drug Alcohol Depend. 116(1-3):142-50

Smoking topography characteristics of heavy cannabis users	20	Cannabis	Smoking characteristics generally were not significantly associated with cognitive performance. Smoking topographymeasures were significantly correlated with self-reported measures of cannabis use, indicating validity of these assessments, but topography measures were more sensitive than self-report in predicting cannabis-related outcomes.	McClure, E. A., Stitzer, M. L., and Vandrey, R. (2012). Characterizing smoking topography of cannabis in heavy users. Psychopharmacology (Berl). 220: 309-318.
Clinical and forensic drug testing. Oral fluid (OF) cannabinoid pharmacokinetics during ad libitum smoking	11 cannabis smokers resided in a closed research unit for 51 days	5-day oral delta-9-tetrahydrocannabinol (THC) treatments	Cannabinoid disposition in OF was highly influenced by Δtime and composition of smoked cannabis. Furthermore, cannabinoid OF concentrations increased over ad libitum smoking days, in parallel with increased cannabis self-administration, possibly reflecting development of increased cannabis tolerance.	Lee D, Vandrey R, Mendu DR, Murray JA, Barnes AJ, Huestis MA (2015) Oral fluid cannabinoids in chronic frequent cannabis smokers during ad libitum cannabis smoking. Drug Test Anal. 7(6):494-501 Lee D, Vandrey R, Milman G, Bergamaschi M, Mendu DR, Murray JA, Barnes AJ, Huestis MA. (2013) Oral fluid/plasma cannabinoid ratios following controlled oral THC and smoked cannabis administration. Anal Bioanal Chem. 405(23):7269-79

THC AEs	Recreational users (N = 24)	Cannabis cigarettes with four doses of THC (placebo 29, 49 and 69 mg of THC)	A cubic relationship was observed between 'feeling the drug' and 'wanting more'. The THC-induced decrease in 'feeling stimulated' and increase in anxiety lasted up to 8 h post-smoking. Sedation at 8 h post-smoking was increased by a factor of 5.7 with the highest THC dose, compared to the placebo.	Hunault CC, Böcker KB, Stellato RK, Kenemans JL, de Vries I, Meulenbelt J. (2014) Acute subjective effects after smoking joints containing up to 69 mg Δ9-tetrahydrocannabinol in recreational users: a randomized, crossover clinical trial. Psychopharmacology (Berl). Dec;231(24):4723-33
Synthetic cannabinoid (SC) AEs	Respondents (N = 42; 88% participation rate) were primarily young adults, male, racially diverse, and high school graduates.	Synthetic cannabinoid (SC) smoking, despite a federal ban on 5 common SCs, which went into effect on March 1, 2011	Common reasons reported for use included, but were not limited to, seeking a new "high" similar to that produced by marijuana and avoiding drug use detection via a positive urine screen. The primary side effects were trouble thinking clearly, headache, dry mouth, and anxiety. No significant differences were found between synthetic cannabinoid product users (ever or current) and nonusers by demographics or other characteristics.	Gunderson EW1, Haughey HM, Ait-Daoud N, Joshi AS, Hart CL. (2014) A survey of synthetic cannabinoid consumption by current cannabis users. Subst Abus. 35(2):184-9

THC AEs (brain morphometry)	MRI scans on young adult recreational marijuana users	Recreational marijuana	Gray matter density analyses revealed greater gray matter density in marijuana users than in control participants in the left nucleus accumbens extending to subcallosal cortex, hypothalamus, sublenticular extended amygdala, and left amygdala, even after controlling for age, sex, alcohol use, and cigarette smoking. Trend-level effects were observed for a volume increase in the left nucleus accumbens only. Significant shape differences were detected in the left nucleus accumbens and right amygdala.	Gilman JM, Kuster JK, Lee S, Lee MJ, Kim BW, Makris N, van der Kouwe A, Blood AJ, Breiter HC. (2014) Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. J Neurosci. 34(16):5529-38
THC AEs on neuropsychological functions	Heavy cannabis users, who had a history of cocaine use (n = 61)	Single doses of cocaine HCl (300 mg), cannabis (THC μg·kg(-1)) and placebo	Single doses of cannabis impaired psychomotor function and increased response errors during impulsivity tasks. Single doses of cocaine improved psychomotor function and decreased response time in impulsivity tasks, but increased errors.	van Wel JH, Kuypers KP, Theunissen EL, Toennes SW, Spronk DB, Verkes RJ, Ramaekers JG (2013) Single doses of THC and cocaine decrease proficiency of impulse control in heavy cannabis users. Br J Pharmacol. 170(7):1410-20

Cannabinoid levels in serum or urine in abstinent chronic cannabis users.	6 chronic, daily cannabis users (one female, five males, average age 30.0 years; BMI 20.8)	Moderate-intensity workout and a 24-hr period of food deprivation; analysed for Δ9-tetrahydrocannabinol (THC) and 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THCCOOH) by liquid chromatography-tandem mass spectrometry (LCMSMS)	There were no major differences in the measured cannabinoid levels in serum or urine before and after physical exercise or food deprivation. We conclude that exercise and/or food deprivation are unlikely to cause sufficient cannabinoid concentration changes to hamper correct interpretations in drug testing programmes.	Westin AA1, Mjønes G, Burchardt O, Fuskevåg OM, Slørdal L. (2014) Can physical exercise or food deprivation cause release of fat-stored cannabinoids? Basic Clin Pharmacol Toxicol. 115(5):467-71

Safety and adverse effects of coadministration of CBD and fentanyl	Healthy volunteers aged 21 to 65 years with prior opioid exposure, regardless of the route	CBD, coadministered with intravenous fentanyl	SAFTEE data were similar between groups without respiratory depression or cardiovascular complications during any test session. After low-dose CBD, tmax occurred at 3 and 1.5 hours in sessions 1 and 2, respectively. After high-dose CBD, tmax occurred at 3 and 4 hours in sessions 1 and 2, respectively. Cannabidiol does not exacerbate adverse effects associated with intravenous fentanyl administration. Coadministration of CBD and opioids was safe and well tolerated.	Manini AF, Yiannoulos G, Bergamaschi MM, Hernandez S, Olmedo R, Barnes AJ, Winkel G, Sinha R, Jutras-Aswad D, Huestis MA, Hurd YL (2015) Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans. J Addict Med. 9(3):204-10
Pharmacokinetics in chronic, daily cannabis smokers who received high-dose oral THC pharmacotherapy and later a smoked cannabis challenge	11 daily cannabis smokers	0, 30, 60, or 120 mg/d THC for four 5-day medication sessions	The significant withdrawal effects noted during placebo dronabinol administration were supported by significant plasma THC and 11-OH-THC concentration decreases. During active dronabinol dosing, significant dose-dependent increases in THC and 11-OH-THC concentrations support withdrawal symptom suppression.	Milman G, Bergamaschi MM, Lee D, Mendu DR, Barnes AJ, Vandrey R, Huestis MA (2014) Plasma cannabinoid concentrations during dronabinol pharmacotherapy for cannabis dependence. Ther Drug Monit. 36(2):218-24

Drug-drug interaction between cannabidiol (CBD) and clobazam (CLB) in refractory epilepsy in children	13 subjects with refractory epilepsy	Cannabidiol (CBD) and clobazam (CLB)	CLB and CBD are both metabolized in the cytochrome P450 (CYP) pathway. Nine of 13 subjects had a >50% decrease in seizures, corresponding to a responder rate of 70%. The increased CLB and nCLB levels and decreases in seizure frequency occurred even though, over the course of CBD treatment, CLB doses were reduced for 10 (77%) of the 13 subjects. Side effects were reported in 10 (77%) of the 13 subjects, but were alleviated with CLB dose reduction	Geffrey AL, Pollack SF, Bruno PL, Thiele EA (2015) Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia. 2015 Jun 26.

Appendix 2: Table of Previously Conducted Trials using Palmitoylethanolamide

Indication & *Trial Design*	**Number of Patients**	**PEA Dosage**	**Main Results**	**Ref**
Sciatic pain *Double-blind, randomized, two doses of PEA vs placebo*	636	1st arm: 300mg/die x 3 weeks 2nd arm: 300mg/bid for weeks	Significant decrease of pain on VAS (from 7 to 2)	G. Guida, A. de Fabiani, F. Lanaia, A. *et al*. La palmitoiletanolamida (Normast) en el dolor neuropatico cronico por lumbociatalgia de tipo compresivo: estudio clinico multicentrico. Dolor 2010; 25: 35-42
Sciatic pain *Double-blind, randomized, two doses of PEA vs placebo*	111	1st arm: 300mg/die for 3 weeks 2nd arm: 300mg/bid for weeks	Significant decrease in the duration of treatment with anti-inflammatory and analgesic drugs	Canteri L *et al*. Reduction of analgesics in patients suffering from lumbosciatic pain, treated with palmitoylethanolamide. Dolor 2010; 25: 227-34.
Pudendal neuralgia *Case Report*	1	300mg/tid gradually decreasing to 300mg/die for1 year	Resolution of chronic pelvic pain	Calabrò RS, Gervasi G, Marino S, *et al*. Misdiagnosed Chronic Pelvic Pain: Pudendal Neuralgia Responding to a Novel Use of Palmitoylethanolamide. Pain Med 2010; 11(5): 781-4.
Diabetic neuropathic pain *Open*	30	300mg/bid for 60 days	Significant reduction of pain, burning, paraesthesia and numbness	Schifilliti C, Cucinotta L, Fedele V, *et al*. Palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients. XIV Congress of the European Shock Society. September, Taormina, Italy 2011.
Postoperative pain (surgical extraction of impacted lower third molars) *Single-blind, randomized, splitmouth*	30	300mg/bid for 6 days before and 9 days after surgery	Significant reduction in pain intensity	Bacci C, Cassetta G, Emanuele B, *et al*. Randomized split-mouth study on postoperative effects of palmitoylethanolamide for impacted lower third molar surgery. ISRN Surg. 2011 2011917350.
TMJ pain caused by osteoarthritis *Double blind randomized vs NSAIDs*	24	300mg at morning + 600mg at evening for7 days; followed by 300mg/bid for 7 days Vs ibupfofen (600 mg/tid for 14 days)	Significant decrease of pain on VAS (from 7 to 0.7) an significant better maximum mouth opening compared to ibuprofen.	Bortolotti F, Russo M, Bartolucci ML, *et al*. Palmitoylethanolamide versus NSAID in the treatment of TMJ's pain. J Orofac Pain
Diabetic neuropathy pain associated with carpal tunnel syndrome *Group-controlled, randomized, PEA treatment v standard care*	50	600 mg/bid for 60 days	Significant relief of pain. Significant improvement of neurophysiologic parameters	Assini A, Laricchia D, Pizzo R, *et al*. The carpal tunnel syndrome in diabetes: clinical and electrophysiological improvement after treatment with palmitoylethanolamide Eur J Neurol 2010; 17(S3): 295.
Carpal tunnel syndrome in diabetic patients *Group-controlled, randomized vs non-treated patients*	40	600mg/bid for 60 days	Significant reduction of pain and functional status. Significant improvement neurophysiologic parameters	Assini A, Laricchia D, Pizzo R, *et al*. Tunnel carpale nel paziente diabetico. Migliloramento clinico ed elettrofisiologico dopo trattamento con palmitoiletanolamide. [Carpal tunnel syndrome in the diabetic patient. Clinical and electrophysiologic improvement after treatment with palmitoylethanolamide]. 34th National Congress AISD – New frontiers in pain medicine. May, Riccione, Italy 2011.
Pain associated with carpal tunnel	26	1st arm: 300mg/bid for 30 days	Significant dose-dependent reduction of pain and improvement of	Conigliaro R, Drago V, Foster PS, *et al*. Use of palmitoylethanolamide in the entrapment neuropathy of the median in the wrist. Minerva

syndrome *Group-controlled, randomized, two doses of PEA vs non-treated patients*		2nd arm: 600mg/bid for 30 days	neurophysiologic parameters compared with control group.	Med 2011; 102(2): 141-7.
Neuropathic pain *Open*	27	300mg/bid for 3 weeks followed by 300mg/die for 4 weeks	Significant reduction of pain and improvement of electrophysiological parameters	Biasiotta A, Di Stefano G, Leone C, *et al*. Efficacy of palmitoylethanolamide in patients with painful neuropathy. A clinical and neurophysiological open study. Preliminary results. Eur J Pain 2010; 4(1): 77.
Low back pain *Open (Combination therapy)*	20	600mg/bid for 30 days + oxycodone	Significant decrease of pain on VAS (from 7 to 2.5)	Desio P. Combination of oxycodone and palmitoylethanolamide for low back pain treatment. Rivista Siared di Anestesia e Medicina Critica 2011; 1(2): 62-71.
Neuropathic chronic pain (Diabetic neuropathy and postherpetic neuralgia) *Open (Combination therapy)*	30	Combination of Pregabalin+ PEA 600mg bid for 45 days + pregabalin	Significant decrease of pain on VAS, from 7.6 to 1.8	Desio P. Associazione tra pregabalin e palmitoiletanolamide per il trattamento del dolore neuropatico. [Association of palmitoylethanolamide and pregabalin in the management of neuropathic pain]. Pathos 2010; 17(4): 9-14.
Various pain states *Open (Combination therapy)*	517	600mg/bid for 3 weeks followed by 600mg/die for 4 weeks + Pregabalin and oxycodone	61% decrease of mean pain score on Numeric Rating Scale	Di Paolo A, Gianfelice V, Silvestri C, *et al*. La palmitoiletanolamide nel trattamento del dolore attivato dal sistema gliale: nostra esperienza. [Palmitoylethanolamide in the management of gliaactivated pain. Our experience] 34th National Congress AISD – New frontiers in pain medicine. May 2011, Riccione, Italy.
Low back pain *Open (Combination therapy)* *Controlled (PEA +standard analgesics group vs standard analgesics only)*	81	600mg/bid for 3 weeks followed by 600mg/die for 4 weeks +/- Standard analgesics	Significant reduction of pain intensity in the PEA group compared to control group	Palomba R, Adfiletta S, Candiello A, *et al*. Multimodal analgesia for chronic pain: rationale and future directions. Naples Pain Conference. Napoli, Italy 2010.
Diabetic neuropathic pain *Group- controlled: Combination of PEA +Pregabalin vs Pregabalin*	74	600mg/bid for 10 days followed by 600mg/die for 20 days followed by 300mg/die for 30 days	Significantly higher rate of responders (i.e., <60% decrease in pain score) in the combination therapy group compared to pregabalin only group.	Adiletta S, Candiello A, Arminio D, *et al*. Pregabalin and Palmitoylethanolamide in diabetic neuropathic pain: an randomized clinical trial. 34th AISD (Italian Association for the Study of Pain) Congress, Riccione, Italy 2011.
Sciatic pain *Group-controlled, randomized, combination of PEA +standard analgesic therapies vs standard analgesic therapies*	85	300mg/bid for 30 days	Significant relief of pain (scored both on VAS and Oswestry Low Back Pain Scale) in the PEA group compared to the analgesic-only group.	Dominguez CM, Diaz Martin AA, Ferrer FG, *et al*. Palmitoiletanolamida (PEA) en lumbociatica en asociacion al tratamiento habitual. [Palmitoylethanolamide in lumbosciatic pain in association with standard therapy] 8th National Congress of the Sociedad Española del Dolor. May Madrid, Spain 2010.
Neuropathic pain and spasticity in post-stroke patients	20	600mg/bid for 60 days followed by 600mg/die for 30 days	Significant decrease of pain and spasticity	Russo G, Parabita M. Decrease of spasticity and pain after stroke due to treatment with PEA. 14th congress European Shock Soc, Taormina, Italy 2011.

Open, controlled PEA + Physiother() *vs group treated with only Physiother)*				
Neuropathic pain associated with multiple sclerosis *Open*	20	300mg/bid for 60 days	Significant decrease of neuropathic pain	Mancardi GL, Infante MT, Capello E, *et al*. Palmitoylethanolamide relieves neuropathic pain associated to multiple sclerosis. XL National Congress of the Italian Neurological Society. Padova, Italy 2009.
Chronic pelvic pain associated with endometriosis/ dysmenorrhoea /interstitial cystitis *Open*	25	200mg/tid (+polydatin 20mg/tid) for 40 days	Significant reduction of pain on VAS (from 6.8 to 1.7). Significant decrease in the use of NSAIDs.	Palomba R, De Simone MG, GIovannini A, *et al*. Use of palmitotlethanolamide (PEA) + polydatin in the chronic pelvic pain. SIAARTI, October 2010, Parma, Italy.
Adolescent primary dysmenorrhoea *Open*	20	400mg/bid (+ polydatin 40mg/bid) for 6 months	70% decrease of pelvic pain	Fulghesu A, Magnini R , Mazzella S, *et al*. Treatment of adolescent dysmenorrhea by a new inhibitor of mast cells-induced inflammation (palmitoylethanolamide + trans polydatin). 16th Congress of Pediatric and Adolescent Gynecology, May Montpellier, France 2010.
Chronic pelvic pain and dyspareunia associated with endometriosis *Open (case series)*	4	200mg/bid (+ polydatin 20mg/bid) for 3 months	Significant decrease of pelvic pain. Significant decrease of dyspareunia. Significant reduction in the use of analgesics.	Indraccolo U, Barbieri F. Effect of palmitoylethanolamidepolydatin combination on chronic pelvic pain associated with endometriosis: preliminary observations. Eur J Obstet Gynecol Reprod Biol 2010; 150(1): 76-9.
Chronic pelvic pain associated with endometriosis *Double blind, ,randomized parallel-group, placebo-controlled*	61	400mg/tid (+ 40mg/tid polydatin) for 3 months Vs celecoxib 200 mg/bid for 7 consecutive days	Significant decrease of cronic pelvic pain, dysmenorrhoea and dyspareunia in the PEA group compared to placebo group	Cobellis L, Castaldi MA, Giordano V, *et al*. Effectiveness of the association micronized N-Palmitoylethanolamine (PEA)-transpolydatin in the treatment of chronic pelvic pain related to endometriosis after laparoscopic assessment: a pilot study. Eur J Obstet Gynecol Reprod Biol 2011; 158: 82-6.
Safety and Efficacy Study of PEA and Polydatin on Intestinal Inflammation and Visceral Hyperalgesia in IBS Patients. *Phase II clinical study by CM&D Pharma Limited/Nestle*	Recruitment status is Recruiting	200 mg Micronised Palmitoylethanolamide (PEA) and 20 mg Polydatin	-	http://clinicaltrials.gov/ct2/show/NCT01370720
Whether the anti-inflammatory agent palmitoylethanolamide (PEA) can counteract the increase of intraocular pressure (IOP) that may occur after neodymium-doped: yttrium aluminum garnet (Nd:YAG) laser iridotomy	15 after bilateral laser iridotomy (Visulas YAG III Laser; Zeiss) for the prevention of primary closed-angle glaucoma.	Pretreatment with placebo or PEA (t0) Visimast 300 mg, Epitech Group Srl	PEA can counteract the increase of IOP that occurs after iridotomy. It is likely that PEA controls the inflammatory process after iridotomy.	Pescosolido N, Librando A, Puzzono M, Nebbioso M. Palmitoylethanolamide effects on intraocular pressure after Nd:YAG laser iridotomy: an experimental clinical study. J Ocul Pharmacol Ther. 2011 Dec;27(6):629-35.
Oral palmitoyl-ethanolamide (PEA) on	42	PEA 300-mg/bid Vs	Systemic administration of PEA reduces IOP in patients with glaucoma and ocular	Gagliano C, Ortisi E, Pulvirenti L, Reibaldi M, Scollo D, Amato R, Avitabile T, Longo A. Ocular hypotensive effect of oral palmitoyl-

intraocular pressure (IOP) in primary open angle glaucoma (POAG) and ocular hypertension (OH). *Randomized, double-blind, crossover clinical trial*		placebo (PEA vehicle tablets bid)	hypertension. PEA could be a valuable tool for the treatment of glaucoma	ethanolamide: a clinical trial. Invest Ophthalmol Vis Sci. 2011 Aug 3;52(9):6096-100.
Vulvodynia and proctodynia. *Case Study*	1	baclofen 5 % and palmitoylethanolamide 400 mg, tid	Topical baclofen and palmitoylethanolamide can be a viable treatment option in chronic vulvodynia and proctodynia.	Keppel Hesselink JM, Kopsky DJ, Sajben NL. Vulvodynia and proctodynia treated with topical baclofen 5 % and palmitoylethanolamide. Arch Gynecol Obstet. 2014 Aug;290(2):389-93.
Chronic regional pain syndrome (CRPS) intractable CRPS type 1 *Case study*	1	PeaPure® 400 mg capsules (JP Russell Sciences Ltd, Nicosia, Cyprus) and topical 10% ketamine cream	The combination of palmitoylethanolamide and ketamine 10% cream reduced pain by more than 50% after 1 month of treatment, and a marked reduction in swelling and skin discoloration was noticed.	Keppel Hesselink JM, Kopsky DJ Treatment of chronic regional pain syndrome type 1 with palmitoylethanolamide and topical ketamine cream: modulation of nonneuronal cells. J Pain Res 2013 Mar 239-45
Atopic Dermatitis *Investigator-blinded, split-body, randomized trial of children and adults with atopic dermatitis*.	43	PEA-containing nonsteroidal cream in combination with the designated midpotency topical corticosteroid twice daily.	PEA-containing nonsteroidal cream demonstrated more rapid clearance than the sides treated twice daily with a topical corticosteroid in combination with a designated moisturizer cream.	James Q. Del Rosso Use of a Palmitoylethanolamide- Containing Nonsteroidal Cream for Treating Atopic Dermatitis: Impact on the Duration of Response and Time Between Flares Cosmetic Dermatology® • APRIL 2007 • VOL. 20 NO. 4
Long-term management of atopic eczema *Multinational, multicentre, observational, non-controlled, prospective cohort study*	2456	Unique lamellar matrix containing N-palmitoylethanolamine (PEA)	Substantial relief of objective and subjective symptoms of atopic eczema after regular skin care with the study cream. The patient-related effectiveness (decline of pruritus and loss of sleep) indicated a gain in quality of life in these patients. The reduced use of topical corticosteroids is important in view of safety and pharmacoeconomic implications in the treatment of atopic eczema.	Eberlein B, Eicke C, Reinhardt HW, Ring J. Adjuvant treatment of atopic eczema: assessment of an emollient containing N-palmitoylethanolamine (ATOPA study). J Eur Acad Dermatol Venereol. 2008 Jan;22(1):73-82.
to compare the supplementation with Sinerga with the supplementation with bacterial extracts, for the effect on the frequency of episodes of respiratory infection that had resulted in a prescription for antibiotics.	167 children, aged 3 to 7 years, of both sexes, with a clinical history of recurrent respiratory infections	Sinerga a nutritional product containing palmitoylethanolamide, bovine colostrum, phenylethylamine and the new generation of probiotic kluyveromyces FM B0399	The results showed a greater reduction in the frequency of respiratory infections with antibiotic therapy in the group of children supplemented with Sinerga than in the group treated with bacterial extracts. In particular, it was observed that 49.3% of the children supplemented with Sinerga, against 5% of those supplemented with extracts, had no infectious episodes requiring the administration of an antibiotic. 100% of subjects supplemented with Sinerga have had no more than two episodes of respiratory infection, while this condition, in the cohort treated with bacterial extracts, was observed in only 51% of cases.	Nigro A, Nicastro A, Trodella R. Retrospective observational study to investigate Sinerga, a multifactorial nutritional product, and bacterial extracts in the prevention of recurrent respiratory infections in children. Int J Immunopathol Pharmacol. 2014 Jul-Sep;27(3):455-60
To determine whether changes in seminal plasma concentrations of the	90 men attending an infertility	Palmitoylethanolamide and OEA extracted from seminal plasma were quantified by ultra high-performance	Palmitoylethanolamide and OEA concentrations in seminal plasma were lower in men with asthenozoospermia and	Amoako AA, Marczylo TH, Elson J, Taylor AH, Willets JM4, Konje JC. Relationship between seminal plasma levels of anandamide congeners

endogenous lipid signaling molecules palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) have significant effects on sperm quality	clinic for semen analysis.	liquid chromatography (HPLC)-tandem mass spectrometry	oligoasthenoteratozospermia compared with men with normal semen parameters. Palmitoylethanolamide and OEA rapidly and significantly improved sperm motility and maintained viability without affecting mitochondria activity in vitro.	palmitoylethanolamide and oleoylethanolamide and semen quality. Fertil Steril. 2014 Sep 8. pii: S0015-0282(14)01394-6