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Cannabinoide zur Behandlung von Demenz?

Prof. Dr. med. Kirsten Müller-Vahl

Oberärztin an der Klinik für Psychiatrie, Sozialpsychiatrie und Psychotherapie der Medizinischen Hochschule Hannover

Mitglied des Sachverständigenausschusses für Betäubungsmittel des Bundesinstituts für Arzneimittel und Medizinprodukte (BfArM)

Gefördert durch Bayerisches Staatsministerium für Gesundheit, Pflege und Prävention

Moderation & Chatroom-Betreuung

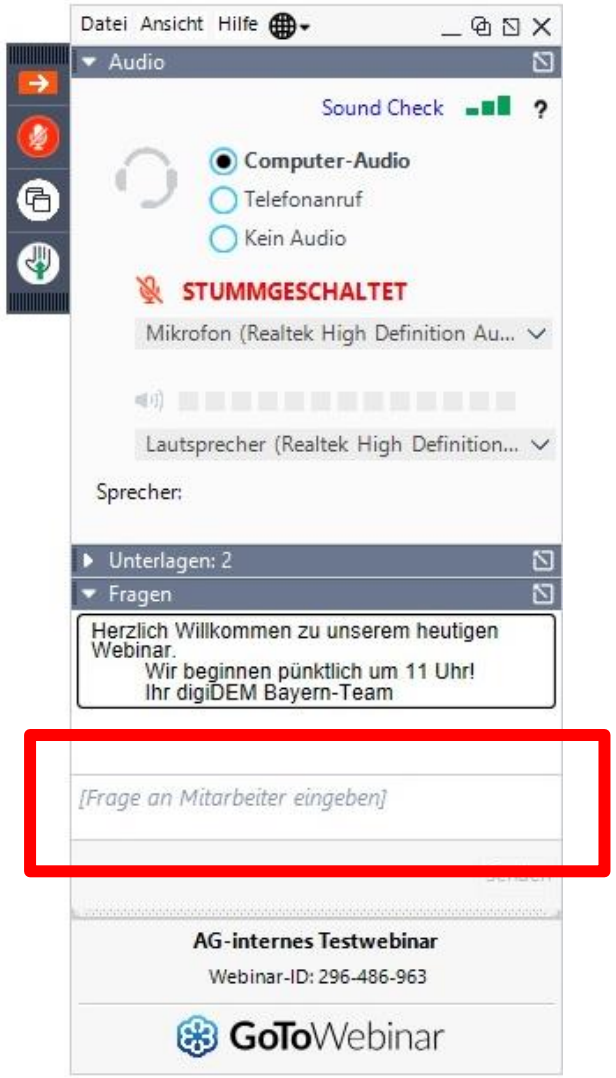
Prof. Dr. Elmar Gräßel

Moderation

Florian Weidinger, M. Sc.

Betreuung Chatroom & Fragen

GoToWebinar – wichtige Funktionen



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Interessenkonflikte

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Consultant's and other honoraria from Abide Therapeutics, adjupharm, Alexion, AlphaSights Ltd., AMP Alternative Medical Products GmbH, Asavita GmbH, Becanex, Boehringer Ingelheim International GmbH, Bionorica Ethics GmbH, CannaMedical Pharma GmbH, Canopy Grouth, Columbia Care, CTC Communications Corp., DHMS Direct Health Medical Services Ltd., Demecan, Enua pharma, DHMS Direct Health Medical Services Ltd., Ethypharm GmbH, Eurox Group, Global Praxis Group Limited, Hormosan Pharma GmbH, Lundbeck, Marry Jane, MCI Germany, Neuraxpharm, Noema Pharma, Sanity Group, Stadapharm GmbH, Synendos Therapeutics AG, Syqe, Tilray, and Zambon.

Advisory/scientific board member for Alexion, Branchenverband Cannabiswirtschaft e.V. (BvCW), CannaMedical Pharma GmbH, Bionorica Ethics GmbH, CannaXan GmbH, Canopy Growth, Columbia Care, Ethypharm GmbH, Hormosan Pharma GmbH, IMC Germany, Leafly Deutschland GmbH, Neuraxpharm, Sanity Group, Stadapharm GmbH, Synendos Therapeutics AG, Syqe Medical Ltd., Therapix Biosciences Ltd., and Tilray.

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Guest editor for Frontiers in Neurology on the research topic “The neurobiology and genetics of Gilles de la Tourette syndrome: new avenues through large-scale collaborative projects”, **Associate editor** for “Cannabis and Cannabinoid Research”, **Editorial Board Member** of “Medical Cannabis and Cannabinoids” und “MDPI-Reports” and a Scientific board member for “Zeitschrift für Allgemeinmedizin”.

Übersicht

- Geschichtliches
- Cannabis-basierte Medikamente
- Indikationen
- Endocannabinoid-System (ECS)
- Wirkweisen Cannabis-basierter Medikamente
  - Tetrahydrocannabinol (THC)
  - Cannabidiol (CBD)
- Leichte kognitive Beeinträchtigung (mild cognitive impairment, MCI), Alzheimer-Demenz
  - Symptomatische Therapie: Tetrahydrocannabinol (THC)
  - Neuroprotektion und Entzündungshemmung: Cannabidiol (CBD)
- Aktuelle und geplante Studien

Journal of Ethnopharmacology
Volume 227, 5 December 2018, Pages 300-315

Review

Cannabis sativa: A comprehensive ethnopharmacological review of a medicinal plant with a long history

Sara Anna Bonini [a], Marika Premoli [a], Simone Tambaro [b], Amit Kumar [c], Giuseppina Maccarinelli [a], Maurizio Memo [a], Andrea Mastinu [a]

8000 – 200 B.C.

- *C. sativa* fiber first appears in Taiwan
- Emperor Shen Neng of China first prescribes medicinal *C. sativa*
- *C. sativa* rope appears in southern Russia
- Herodotus's Histories mention hemp fabrics and use of cannabis by Scythian
- *C. sativa* rope appears in Greece.

200 B.C. – 200 A.D.

- Pliny the Elder's The Natural History mentions hemp rope and marijuana analgesic effects
- Plutarch mentions Thracians using cannabis as an intoxicant
- Discorides, a physician in Nero's army, lists medical marijuana in his pharmacopoeia
- Greek physician Galen prescribes marijuana as a medicine

200 – 1500 A.D.

- Chinese surgeon Hua T`o uses *C. sativa* as anesthetic

- French queen Arnegunde is buried with hemp cloth
- Vikings take hemp rope and seeds to Iceland
- Hasan-ibn-Sabah recruits assassins with hashish

- 1001 Nights, an Arabian collection of tales, describes hashis's intoxicating properties

1500 – 1800 A.D.

- Portuguese physician Garcia da Orta reports *C. sativa* effects
- China's Li Shih-Chen writes of antibiotic and antiemetic effects of *C. sativa*
- Linnaeus classifies *Cannabis sativa*
- Lamarck classifies the plant *Cannabis indica*
- Napoleon's soldiers learn of *cannabis* and hashish in Egypt

1800 – 1950 A.D.

- Irish physician O'Shaughnessy publishes *cannabis* research in English medical journal

- French author Gautier publishes The Hashish Club
- French physician Moreau publishes Hashish and Mental Illness

- Marijuana Tax Act passes, requiring special fees for prescriptions of the drugs

- *C. sativa* removed from U.S. Pharmacopoeia

1950 A.D. – To date

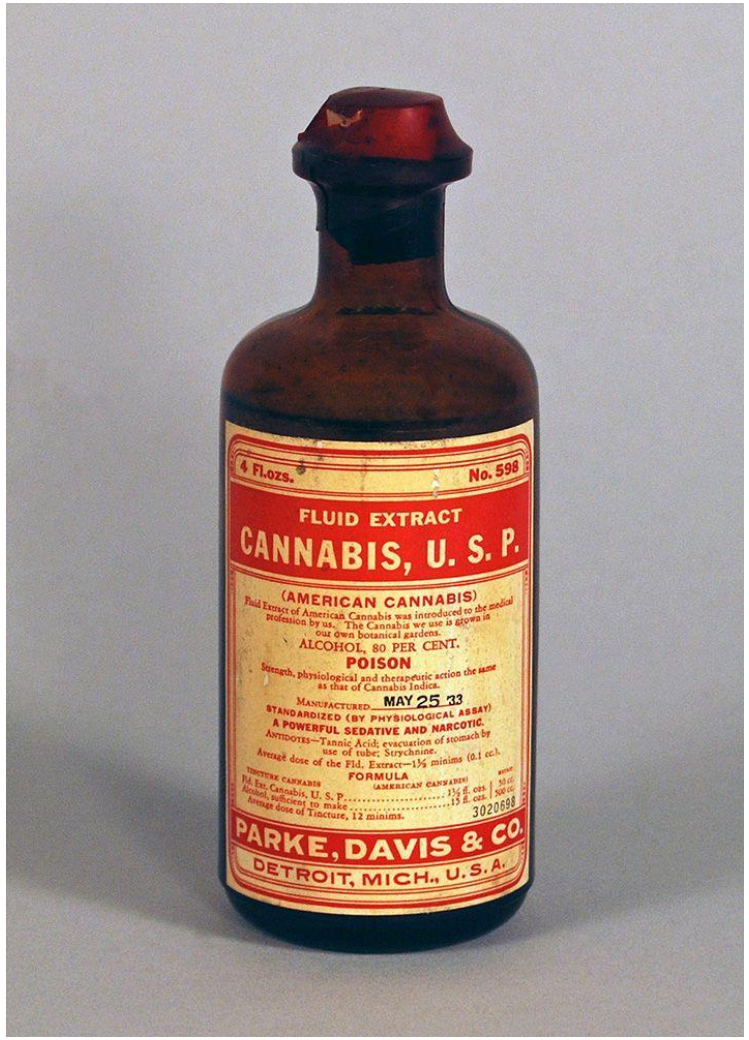
- Czech researchers confirm antibiotic and analgesic effects of *cannabis*
- Gaoni and Mechoulam isolated and synthesized the main phytocannabinoid, D9-THC
- FDA approves dronabinol, a synthetic D9-THC for cancer patients
- FDA approves dronabinol for AIDS-wasting syndrome
- Many Western countries adopt laws in support of medical *C. sativa* uses

Benediktinerin Hildegard von Bingen (1098 – 1179)

- züchtete Cannabis in ihrem Kräutergarten
- „Physica – Liber simplicis medicinae“
- Cannabis…
  - schmerzstillend
  - verdauungsfördernd
  - zur lokalen Behandlung von Geschwüren und Wunden
  - bei rheumatischen und bronchialen Erkrankungen
  - bei Magenbeschwerden und Übelkeit

Stiftung Juliusspital Würzburg

Aufbewahrungsflaschen für Cannabis um 1900



Cannabis sativa

Inhaltsstoffe: > 500

Cannabinoide: > 115

Wichtigste Cannabinoide:

- **Delta-9-Tetrahydrocannabinol (THC)**
- **Cannabidiol (CBD)**
- Cannabichromen (CBC)
- Cannabigerol (CBG)
- Cannabinol (CBN)
- Andere

Andere Bestandteile: Stickstoffverbindungen, Aminosäuren, Proteine, Zucker, Hydrocarbone, Alkohole, Fettsäuren, Ester, Terpene, Flavonoide

Cannabinoid-haltige Arzneimittel

Substanz	Inhaltstoff	BtM-pflichtig	Fertig-arzneimittel	Rezeptur-arzneimittel
Dronabinol	Tetrahydrocannabinol (THC)	-	Marinol® (USA) Syndros® (USA)	**Dronabinol**
Nabilon	Nabilon	**+**	**Canemes® (Kapseln)**	-
Nabiximols	Cannabisextrakt standardisiert auf THC:CBD (1:1)	**-**	**Sativex® (Spray)**	-
Cannabisextrakte	standardisiert auf THC:CBD	**-**	**-**	**Ca. 70 Vollextrakte**
Cannabisblüten	Blüten standardisiert auf THC und CBD	-	-	**Ca. 800 Sorten**
Cannabidiol	Cannabidiol (CBD)	-	-	**CBD**
CBD(-Extrakt)	CBD-Gehalt: 98% THC-Gehalt < 0,2%	**-**	**Epidyolex®**	Individuell in Apotheke herstellbar

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Gesicherte Indikationen: Zulassungen

Indikation	Substanz	Zulassung
Therapie resistente Spastik bei Multipler Sklerose (MS)	**Sativex® (Nabiximols, Cannabisextrakt THC:CBD=1:1)**	**D, >20 weitere europäische Länder**
Übelkeit und Erbrechen unter Chemotherapie bei Tumoren	**Canemes® (Nabilon, THC-Analogon)**	**Deutschland und andere Länder**
Epilepsie: Dravet-Syndrom, Lennox-Gastaut-Syndrom, tuberöse Hirnsklerose	**Epidyolex® (Cannabidiol, CBD)**	**Deutschland und andere Länder**
Therapie von Anorexie mit Gewichtsverlust bei AIDS	Marinol® (THC), Cesamet® (Nabilon)	USA USA
Behandlung von Übelkeit und Erbrechen bei Chemotherapie in der Krebsbehandlung	Marinol® (THC) Cesamet® (Nabilon)	USA USA
Neuropathische Schmerzen	Sativex® (Nabiximols)	Neuseeland, Canada, Israel
adjuvante Schmerztherapie bei fortgeschrittenen Tumorerkrankungen	Sativex® (Nabiximols)	Canada

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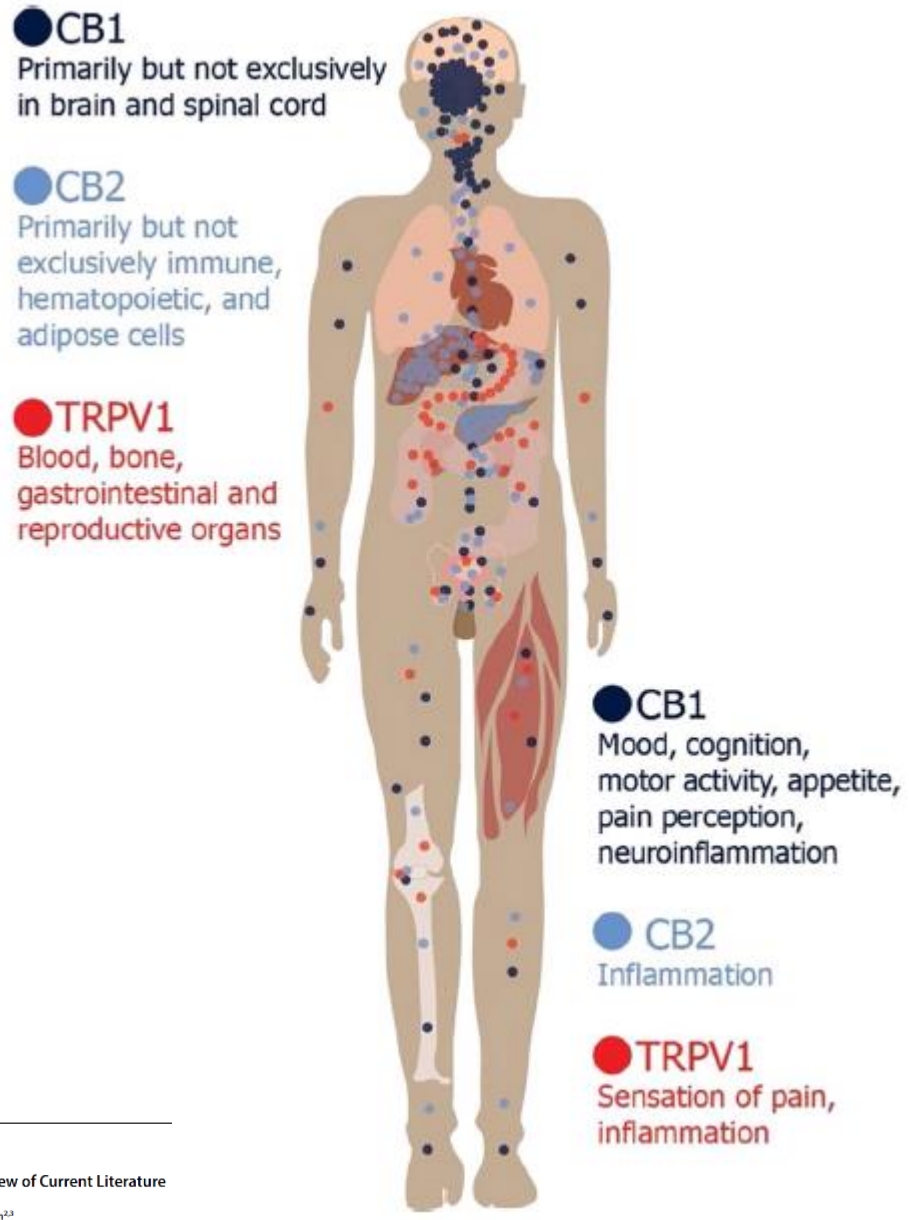
Endocannabinoid-System



Curr Rheumatol Rep (2022) 24:119–131
https://doi.org/10.1007/s11926-022-01065-7

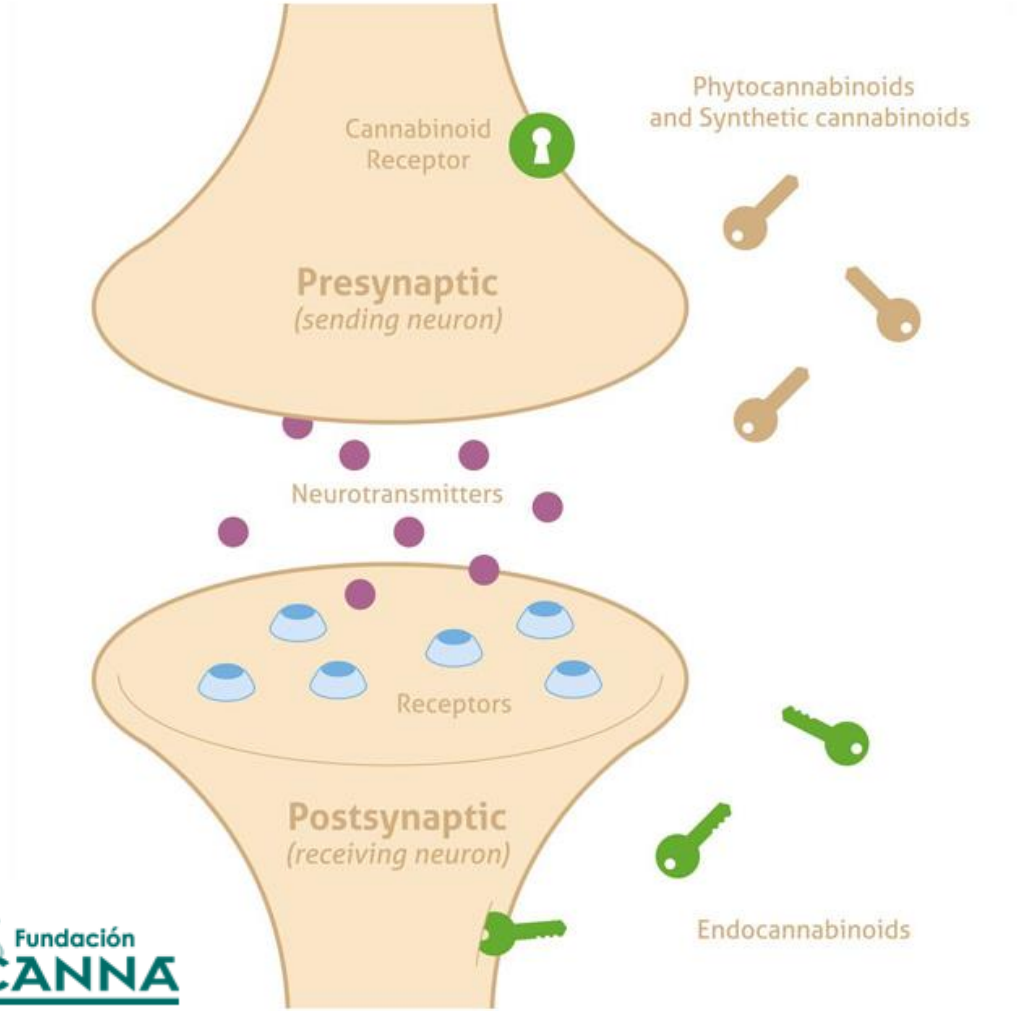
CHRONIC PAIN (R STAUD, SECTION EDITOR)

Cannabis for Rheumatic Disease Pain: a Review of Current Literature

William Benjamin Nowell[1] · Kelly Gavigan[1] · Stuart L. Silverman[2,3]

Fig. 1 Endocannabinoid and other cannabinoid-responsive receptors involved in mechanisms of pain. As described on the upper left, the anatomic distribution varies for cannabinoid receptors 1 and 2 (CB1 and CB2) and the capsaicin receptor (TRPV1), which is responsive to cannabinoids. The physiologic effects of cannabinoids at these receptors vary as well, as described on the right, with CB1 activation affecting mood, cognition, motor activity, appetite, and pain perception; TRPV1 affecting pain sensation; and all three of these receptors involved in inflammatory responses

Endocannabinoid-System: CB1, CB2



- Cannabinoid-Rezeptoren
  - **CB1**
  - **CB2**
  - …..
- Endocannabinoide
  - **Anandamid**=N-Arachidonoyl-Ethanolamin **(AEA)**
  - 2-Arachidonoyl-Gylcerol **(2-AG)**
  - ……

International Journal of
Molecular Sciences

MDPI

Review

A Guide to Targeting the Endocannabinoid System in Drug Design

Adam Stasiulewicz [1,2,*], Katarzyna Znajdek [2,3], Monika Grudzień [1], Tomasz Pawiński [1] and Joanna I. Sulkowska [2,4,5,*]

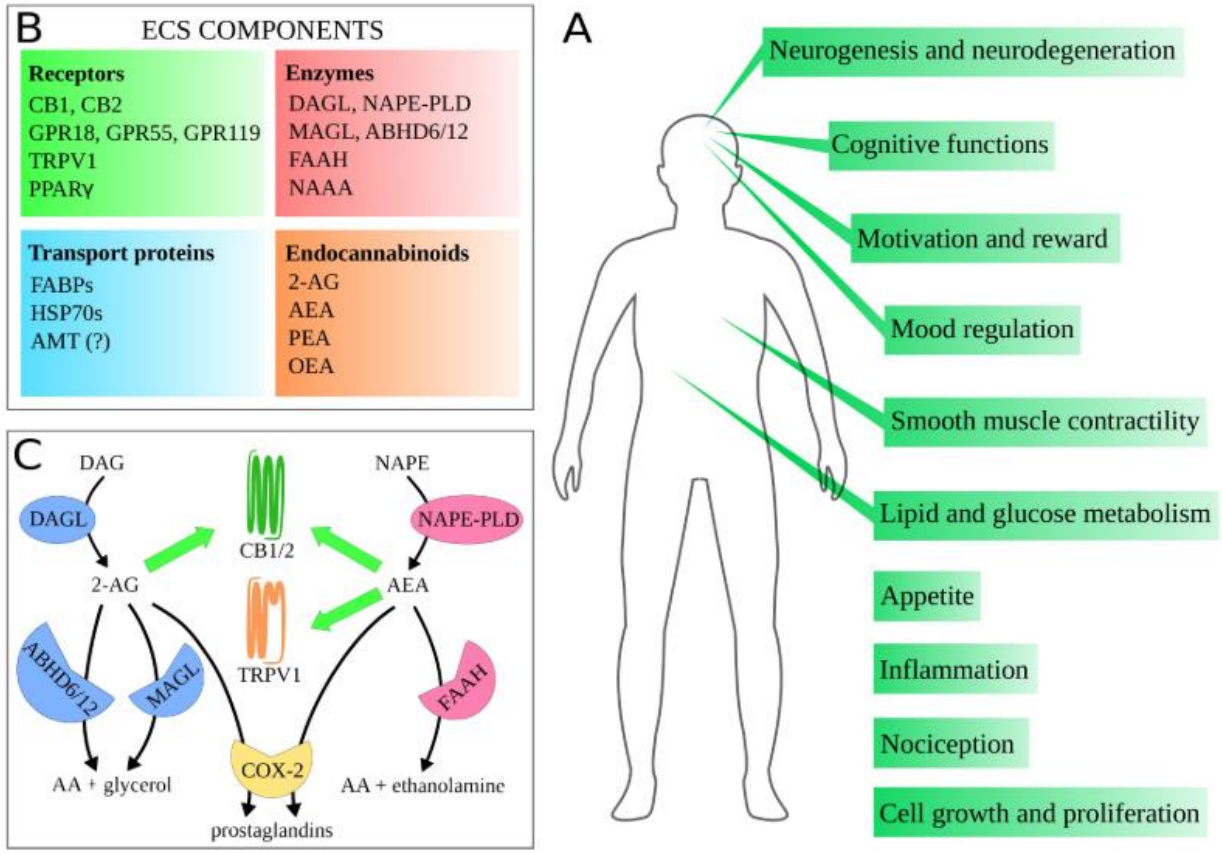
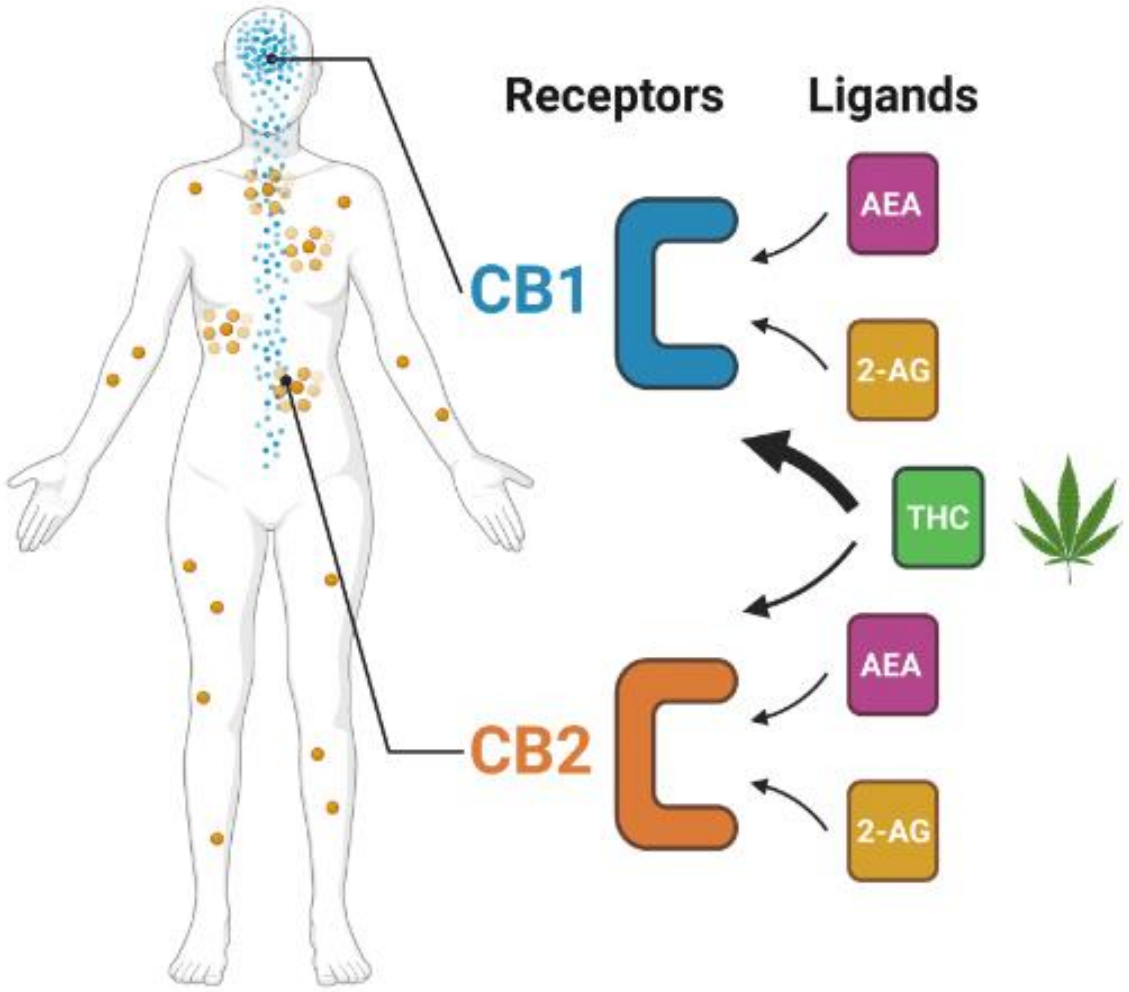


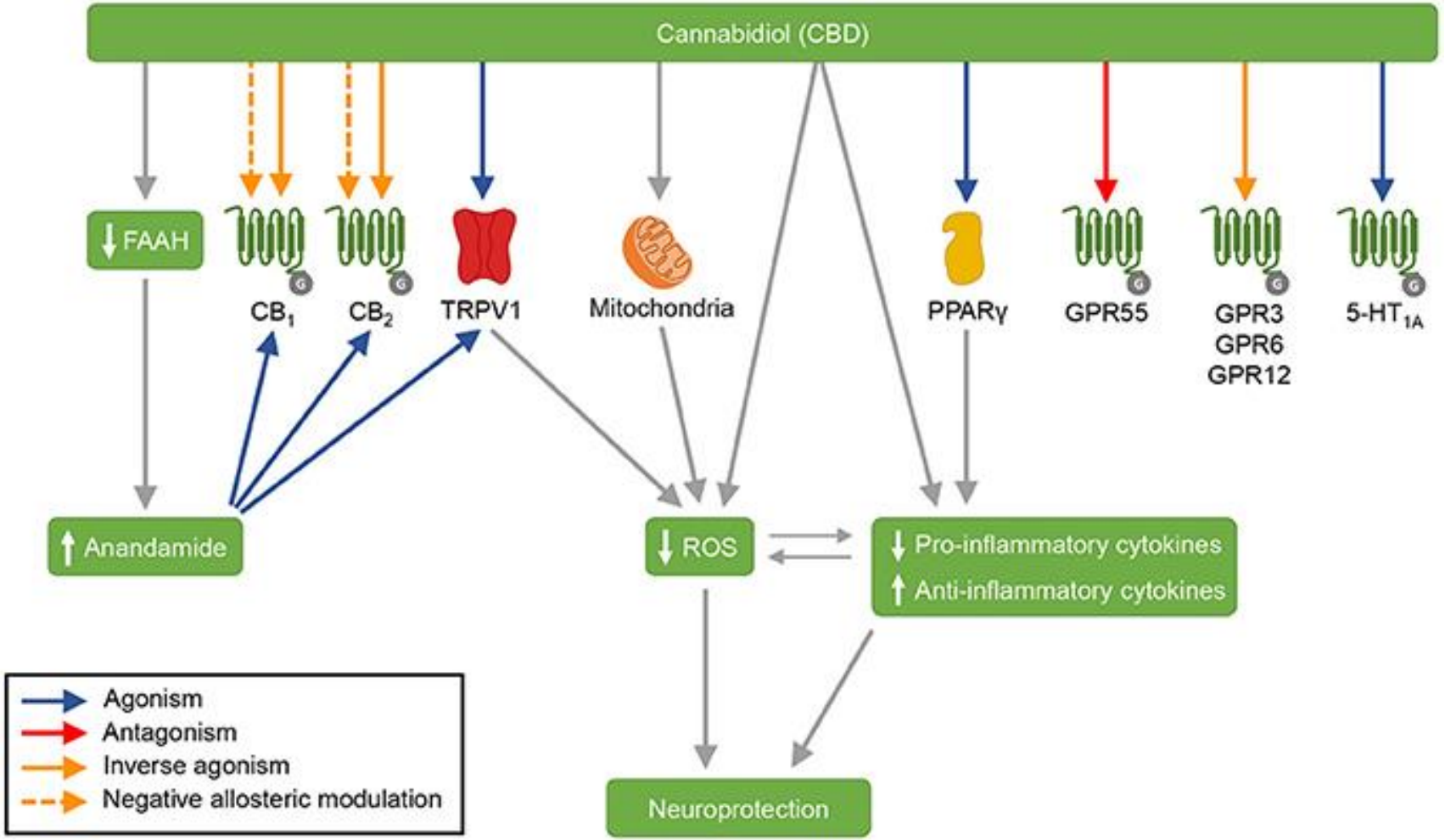
Figure 1. (**A**) physiological processes and functions that the endocannabinoid system (ECS) takes part in. In this figure, we gathered probably the most crucial ones in terms of potential therapeutic applications, described in detail in this review; (**B**) components of the ECS; (**C**) simplified biochemical pathways of the two main endocannabinoids: 2-arachidonoylglycerol (2-AG) and N-arachidonoylethanolamine, also called anandamide (AEA). Blue shapes depict enzymes associated mainly with 2-AG, pink ones—with AEA. Green arrows indicate activation of specific receptors by the endocannabinoids. Abbreviations: 2-AG, 2-arachidonoylglycerol; AA, arachidonic acid; ABHD6/12, α/β hydrolase domain 6 or 12; AEA, N-arachidonoylethanolamine (anandamide); AMT, anandamide membrane transporter; CB1/2, cannabinoid receptor type 1 or 2; COX-2, cyclooxygenase 2; DAG, diacylglycerol; DAGL, diacylglycerol lipase; FAAH, fatty acid amide hydrolase; FABPs, fatty-acid-binding proteins; GPR18/55/119, G protein-coupled receptor 18 or 55 or 119; HSP70s, 70 kilodalton heat shock proteins; MAGL, monoacylglycerol lipase; NAAA, N-acylethanolamine acid amidase; NAPE, N-acylphosphatidylethanolamine; NAPE-PLD, N-acylphosphatidylethanolamine-hydrolyzing phospholipase D; OEA, oleoylethanolamine; PEA, palmitoylethanolamide; PPARγ, peroxisome proliferator-activated receptor γ; TRPV1, transient receptor potential vanilloid type 1 channel.

Wirkungen von THC



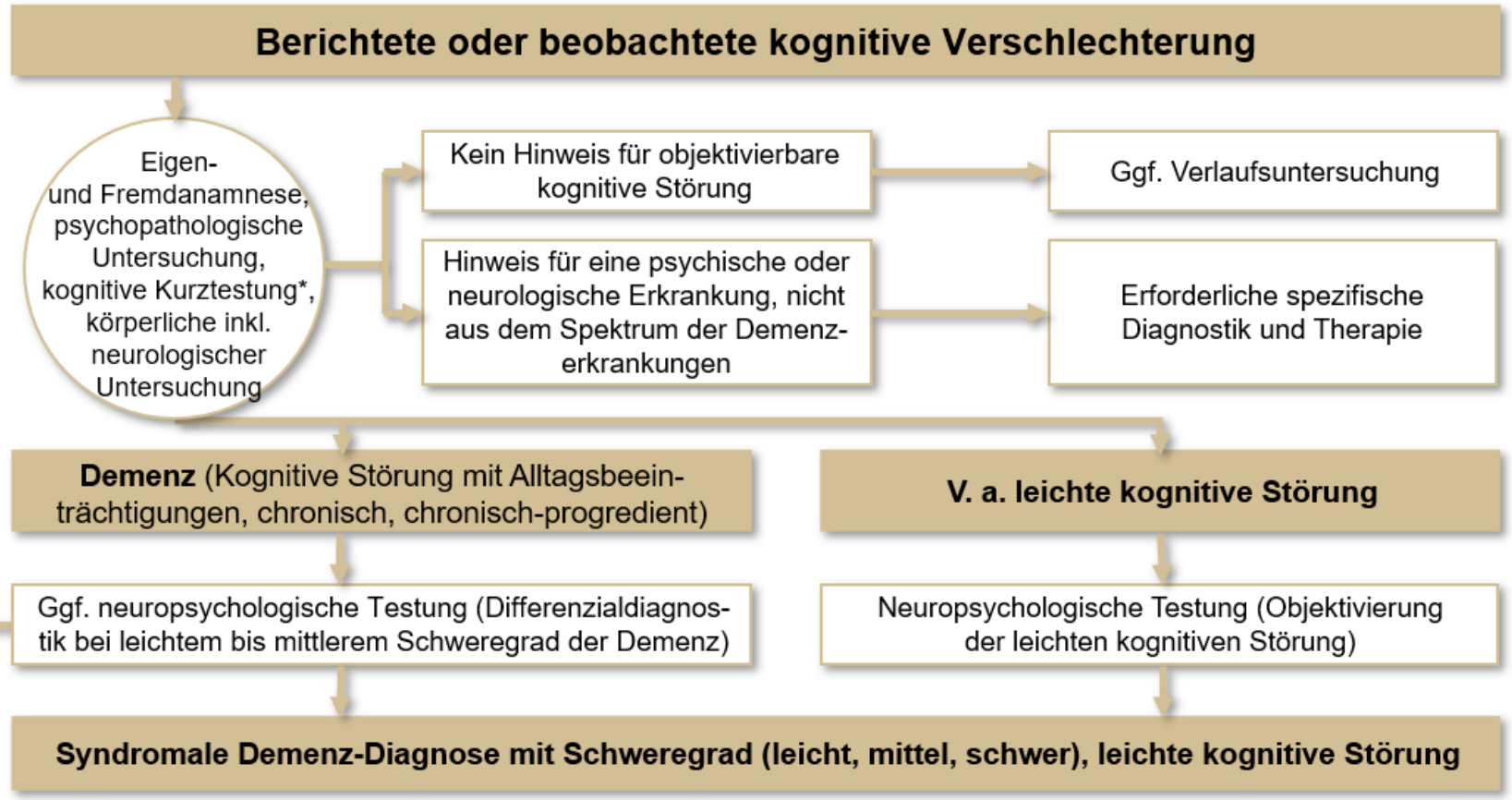
Uthayakumaran K, Sunil M, Ratcliffe EM. Evaluating the Role of the Endocannabinoid System in Axon Guidance: A Literature Review. Cannabis Cannabinoid Res. 2024 Feb;9(1):12-20. doi: 10.1089/can.2023.0138. Epub 2024 Jan 4. PMID: 38174983.

Wirkungen von CBD



Peres FF, Lima AC, Hallak JEC, Crippa JA, Silva RH, Abílio VC. Cannabidiol as a Promising Strategy to Treat and Prevent Movement Disorders? Front Pharmacol. 2018 May 11;9:482. doi: 10.3389/fphar.2018.00482. PMID: 29867488; PMCID: PMC5958190.

Diagnose: Demenz versus MCI

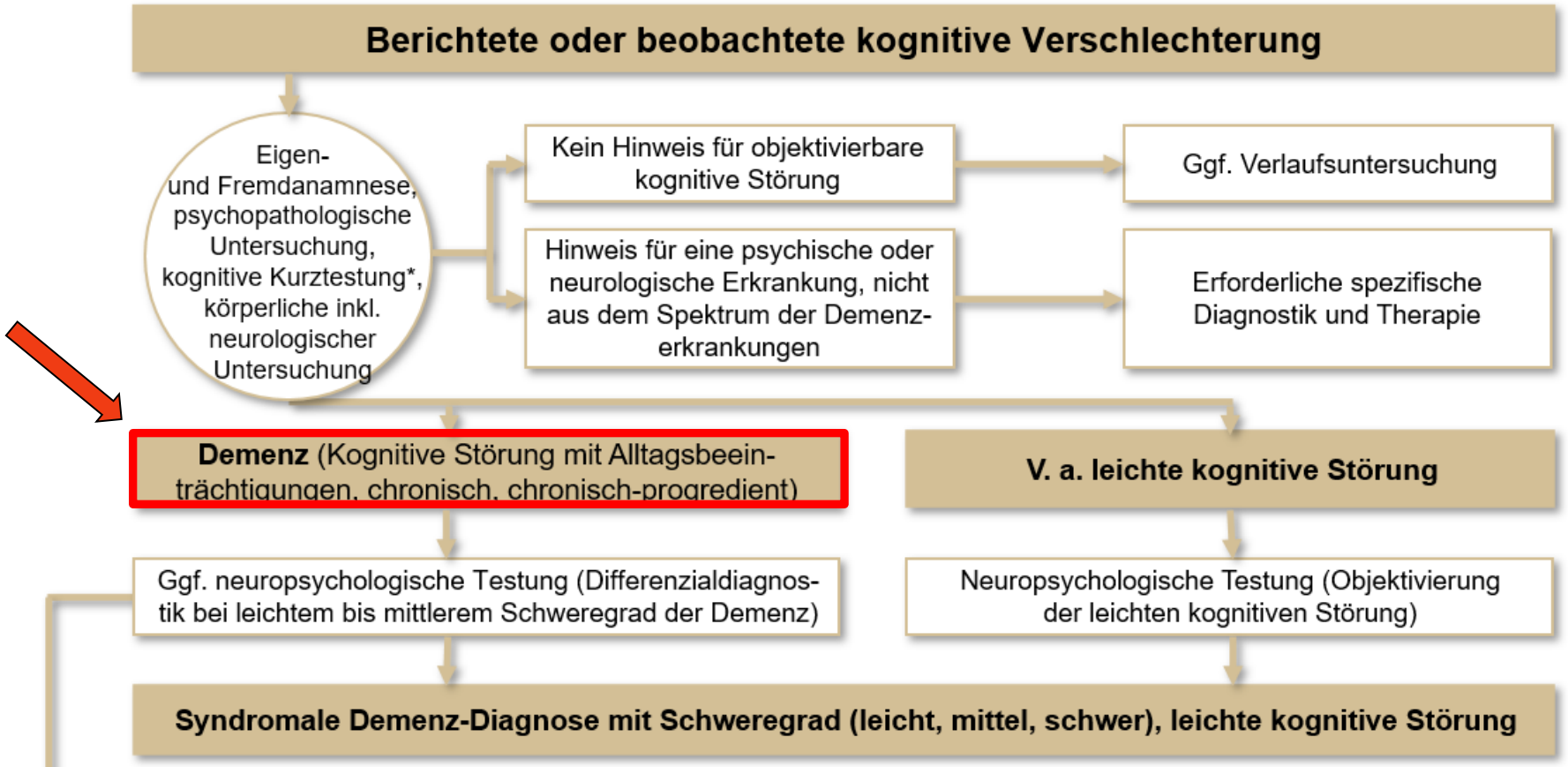


1 **Syndrom-Diagnose** (nicht spezialisiertes Setting)

1 **Syndrom-Diagnose** (spezialisiertes Setting)

* z.B. MMST oder MoCA (insbesondere bei leichter Beeinträchtigung). Abbildung 3: Schematische Darstellung zur Diagnostik. 1) DGN e. V. & DGPPN e. V. (Hrsg.) S3-Leitlinie Demenzen, Version 4.0, 28.11.2023, verfügbar unter: https://register.awmf.org/de/leitlinien/detail/038-013 (Zugriff am 30.11.2023).

Diagnose: Demenz versus MCI



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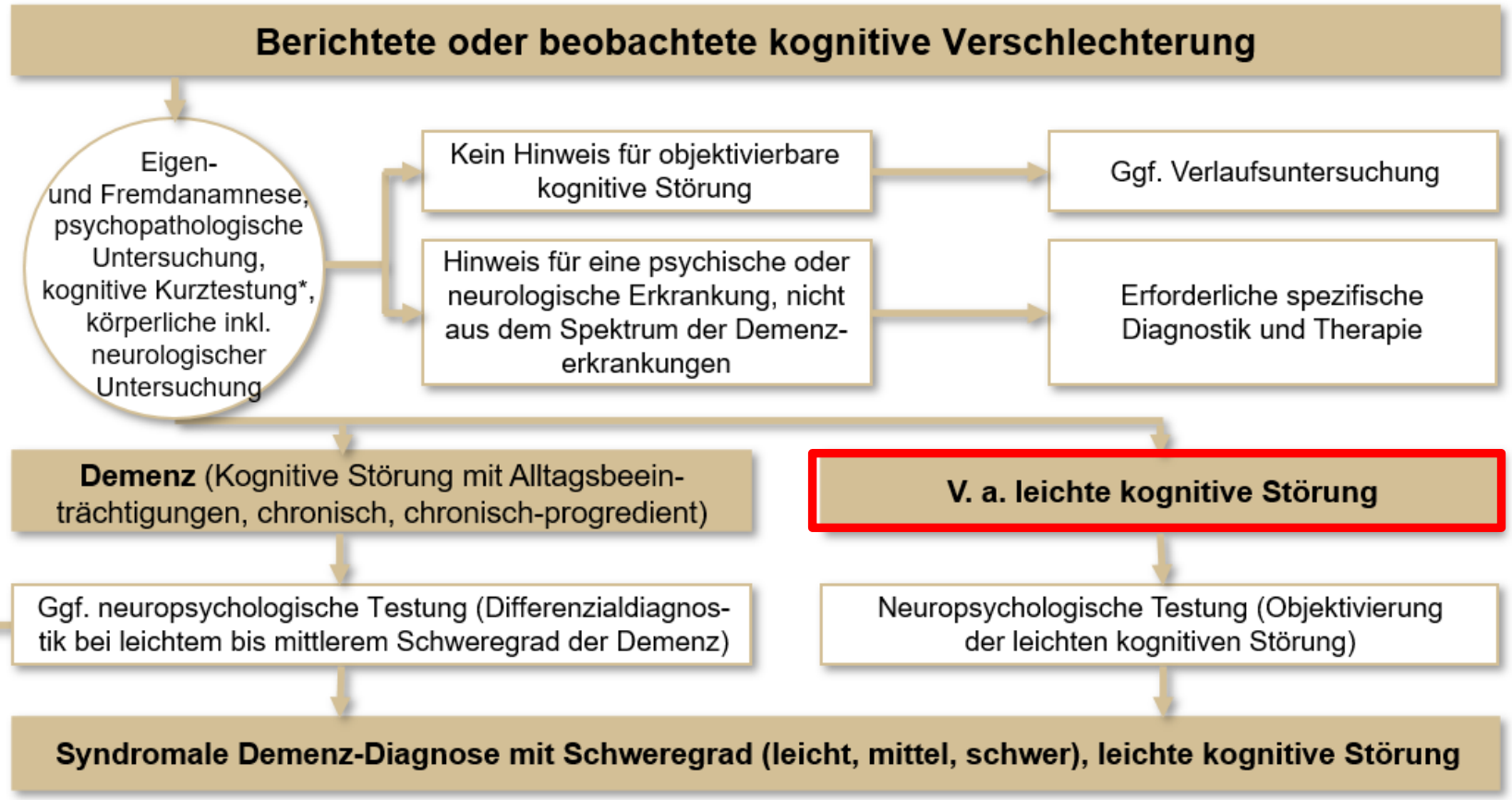

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MCI – MoCA-Test

S3-Leitlinie

Kognitive Kurztests

- Wir empfehlen, einen kognitiven Kurztest (z. B. **MMST, MoCA**) bei selbst berichteten kognitiven Beschwerden – auch auf aktive Nachfrage – oder anderen Hinweisen für eine Demenz nach Einwilligung der betroffenen Person für die Objektivierung einer kognitiven Störung durchzuführen.[2]

Empfehlung 17: Empfehlungsgrad: ⇑⇑ **Stark dafür (A);** Evidenz für Sensitivität, Spezifität, positive und negative Likelihood Ratio für die Diagnose einer Demenz: **Hoch** ⊕⊕⊕⊕; **97 % (starker) Konsens**

MoCA > MMST

- Wir schlagen vor, zur Objektivierung einer leichtgradigen kognitiven Störung wegen höherer Sensitivität **eher den MOCA als den MMST** einzusetzen.[3-5]
- Es gibt weitere Tests, die in Bezug auf eine leichte Beeinträchtigung z. B. im Rahmen einer Alzheimer-Krankheit eingesetzt werden können. Hierzu zählt im deutschen Sprachraum z. B. der **DemTect.**[3-5]

Empfehlung 18: Empfehlungsgrad: ⇑ **Schwach dafür (B);** Evidenz für Sensitivität, Spezifität, Positiver und Negativer Prädiktiver Wert, Likelihood Ratios für die Diagnose von amnestisches MCI im Vergleich zur klinischen Goldstandard-Diagnose: **Moderat** ⊕⊕⊕⊖; **90 % Konsens**

MMST: Mini-Mental Status Test; MoCA: Montreal Cognitive Assessment.

1) DGN e. V. & DGPPN e. V. (Hrsg.) S3-Leitlinie Demenzen, Version 4.0, 28.11.2023, verfügbar unter: https://register.awmf.org/de/leitlinien/detail/038-013 (Zugriff am 30.11.2023). 2) Tsoi KK et al. JAMA Intern Med. 2015;175(9):1450-8. 3) Ozer S et al. J Geriatr Psychiatry. 2016;31(11):1139-1150. 4) Kalbe E et al. Int J Geriatr Psychiatry. 2004;19(2):136-143. 5) Park J, Jeong E, Seomun G. J Adv Nurs. 2018;74(12):2742-2754.

Biomarker-gestützte ätiologische Zuordnung: Alzheimer-Pathologie

3 Biomarker-gestützte Diagnostik

Zur Bestätigung einer **Alzheimer-Pathologie**

Liquordiagnostik

- Zum Ausschluss entzündlicher ZNS-Erkrankungen
- Zur **Bestätigung oder zum Ausschluss einer Alzheimer-Pathologie:**
  - Verhältnis $A\beta_{42/40}$ bevorzugt gegenüber $A\beta_{42}$ allein
  - Verhältnis $A\beta_{42}$/pTau oder $A\beta_{42}$/tTau

Bei unklaren Befunden

Amyloid-PET

Bei V. a. Alzheimer-Krankheit

FDG-PET

Alternative: Perfusions-SPECT

S3-Leitlinie

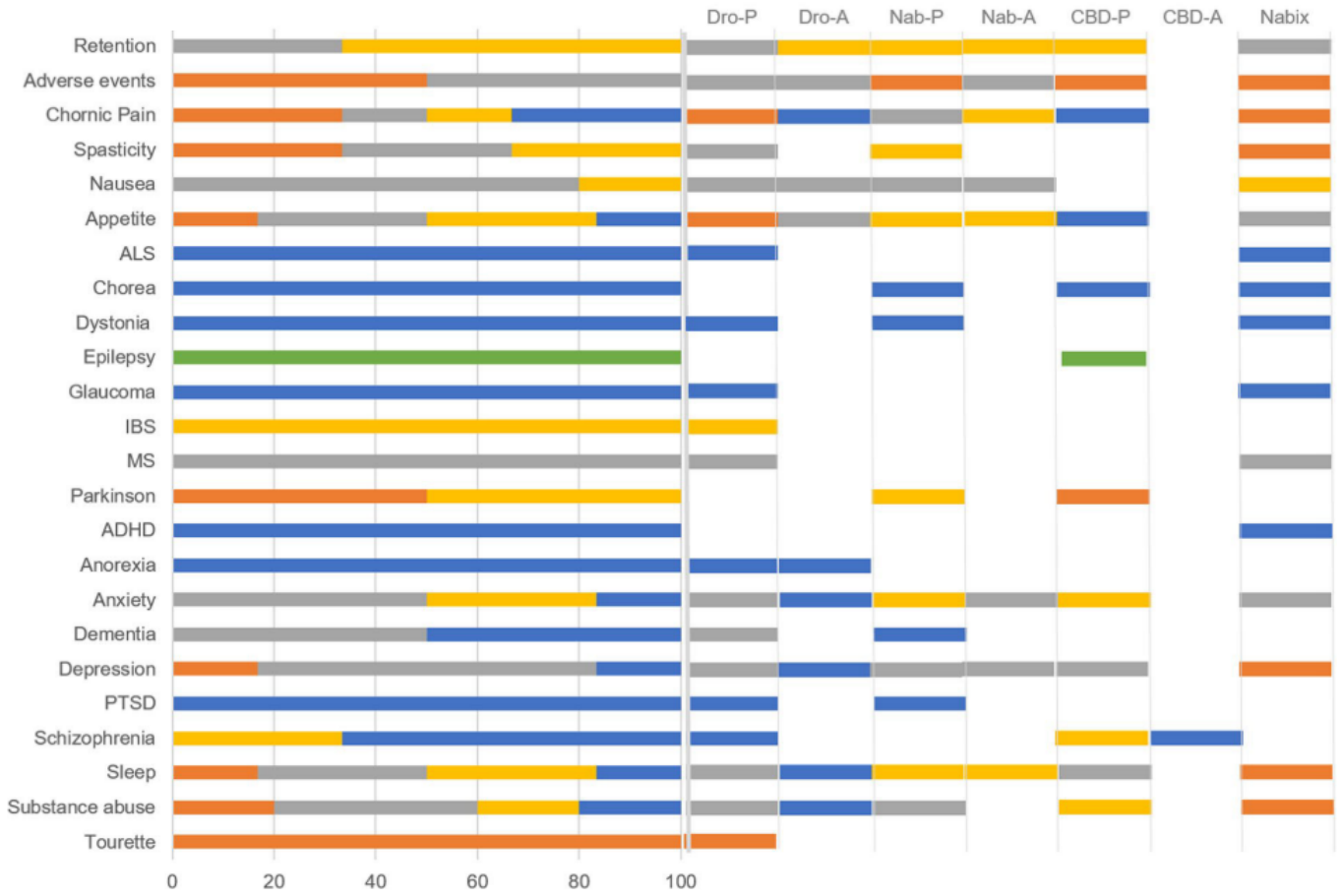
Zur Erkennung oder zum Ausschluss einer Alzheimer-Pathologie,

- **wenn die Ursache einer Demenz oder leichten kognitiven Störung unklar ist**
  - nach Ausschluss reversibler Ursachen
  - nach klinischer und neuro-psychologischer Untersuchung
  - PET: nach ggf. Liquor-Biomarkern
- und ein **Effekt auf das klinische Management** zu erwarten ist

PET: Positronen-Emissions-Tomographie; SPECT: Single-Photon-Emissionscomputertomographie; FDG: Fluordesoxyglukose; Aβ: β-Amyloid; pTau: phosphoryliertes Tau; tTau: Gesamt-Tau.
Modifiziert nach: 1) DGN e. V. & DGPPN e. V. (Hrsg.) S3-Leitlinie Demenzen, Version 4.0, 28.11.2023, verfügbar unter: https://register.awmf.org/de/leitlinien/detail/038-013 (Zugriff am 30.11.2023).

Evidenz: Cannabisarzneimittel

GRADE summary graph:
Percentage of studies showing high, moderate, low, very low evidence and single RCTs for outcome.



Medical cannabinoids:
a pharmacology-based systematic review and meta-analysis for all relevant medical indications

Bilbao and Spanagel *BMC Medicine* (2022) 20:259
https://doi.org/10.1186/s12916-022-02459-1

Medizinische Hochschule Hannover

Evidenz: Cannabisarzneimittel

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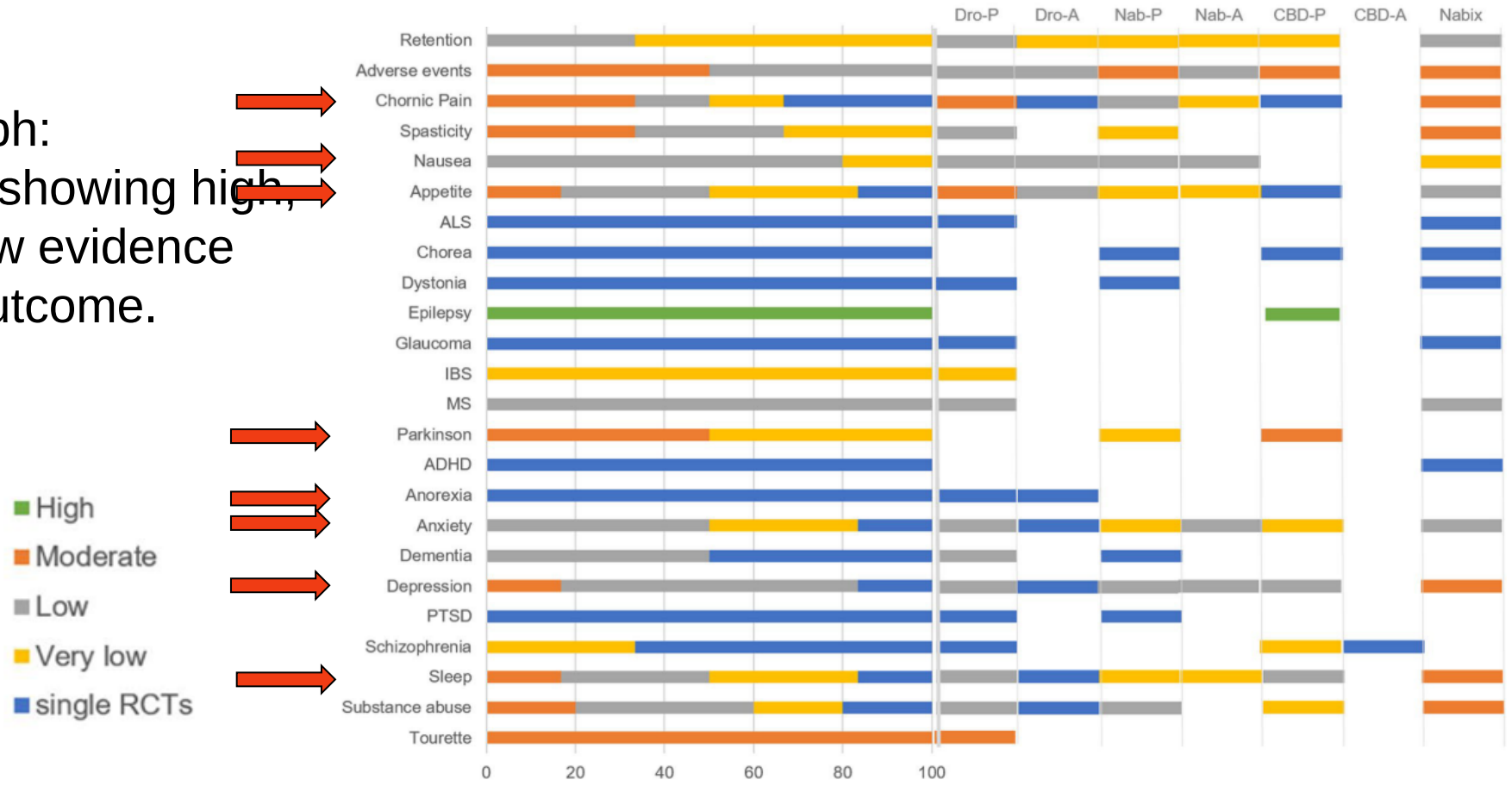

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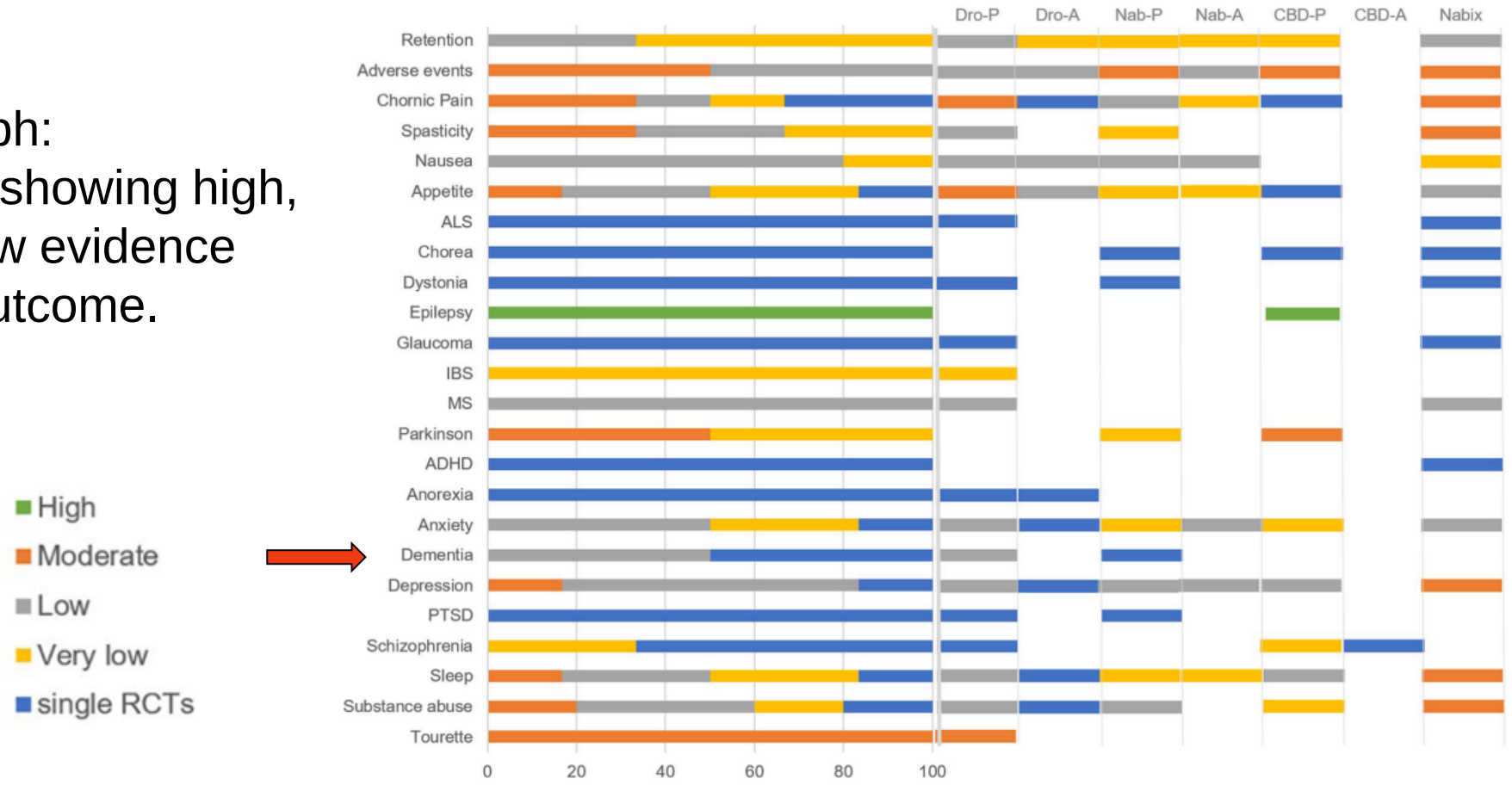

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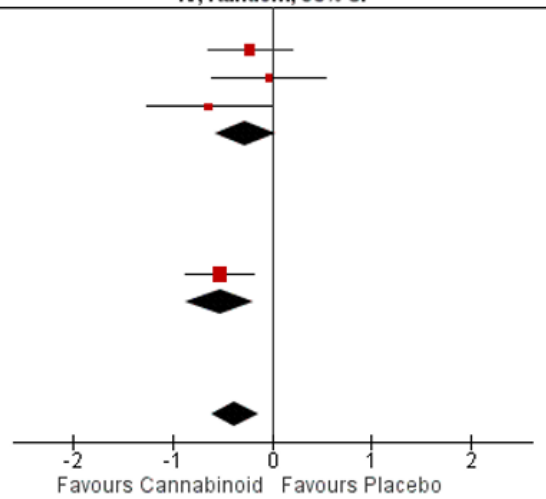
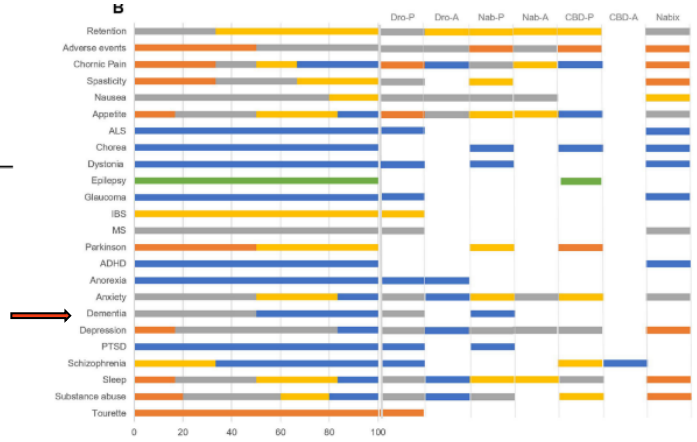
Supplementary Figure 18. Forest plot for dementia

Study or Subgroup	Std. Mean Difference	SE	Cannabinoid Total	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
9.4.2 Dronabinol vs Placebo						
van den Elsen 2015	-0.2217	0.2158	22	22	28.3%	-0.22 [-0.64, 0.20]
van den Elsen 2015b	-0.0301	0.2918	23	24	16.4%	-0.03 [-0.60, 0.54]
Volicer 1997	-0.6354	0.3165	12	12	14.1%	-0.64 [-1.26, -0.02]
Subtotal (95% CI)			**57**	**58**	**58.8%**	**-0.27 [-0.57, 0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 2.06, df = 2 (P = 0.36); I² = 3%						
Test for overall effect: Z = 1.72 (P = 0.09)						
9.4.3 Nabilone vs Placebo						
Herrmann 2019b	-0.5259	0.1731	38	38	41.2%	-0.53 [-0.87, -0.19]
Subtotal (95% CI)			**38**	**38**	**41.2%**	**-0.53 [-0.87, -0.19]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.04 (P = 0.002)						
Total (95% CI)			**95**	**96**	**100.0%**	**-0.37 [-0.61, -0.13]**
Heterogeneity: Tau² = 0.01; Chi² = 3.34, df = 3 (P = 0.34); I² = 10%						
Test for overall effect: Z = 3.05 (P = 0.002)						
Test for subgroup differences: Chi² = 1.25, df = 1 (P = 0.26), I² = 20.2%						





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Medizinische Hochschule Hannover

Dronabinol bei geriatrischen Schmerz- und Palliativpatienten

Eine retrospektive Auswertung der ambulanten kassenärztlichen Therapie

Christoph Wendelmuth[1] · Stefan Wirz[2] · Misel Torontali[1] · Anne Gastmeier[1] · Knud Gastmeier[1]

Ergebnisse. Durch den Einsatz von Dronabinol erreichten 21 der 40 ausgewerteten geriatrischen Patienten (52,5 %) eine Schmerzlinderung von mehr als 30 %, 10 % der Patienten von mehr als 50 %. Im Durchschnitt wurden etwa 4 Symptome oder Nebenwirkungen der Vortherapie positiv beeinflusst. 26 % der Patienten gaben Nebenwirkungen an. Die Ablehnungsquoten betrugen 38,7 % (Gruppe A) bzw. 10,3 % (Gruppe B).

Schmerz
https://doi.org/10.1007/s00482-019-00408-1

Tab. 3 Positive Effekte der Dronabinoltherapie bei den erfassten geriatrischen Patienten, $n = 50$

Symptome und vorbestehende unerwünschte Therapiewirkungen	Anzahl der Patienten mit Verbesserung der Symptome unter Dronabinoltherapie	%
Schwindel	28	56
Stimmung	25	50
Reizbarkeit	23	46
Muskelverspannung	22	44
Schlaf	22	44
Tagesaktivität	22	44
Appetit	12	24
Depressivität	11	22
Benommenheit	9	18
Schwitzen	6	12
Übelkeit	6	12
Obstipation	5	10
Spasmen	5	10
Unruhe	4	8
10 weitere vorbestehende Symptome oder Nebenwirkungen	15	30

Palliativmedizin

JOURNAL OF PALLIATIVE MEDICINE
Volume 25, Number 5, 2022

DOI: 10.1089/jpm.2021.0577

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Integrated Medical Cannabis Consultations in a Palliative Care Program: Policies, Procedures, and Progress after Six Years of Practice

David Lazris, BA,[1] Dhruv Gaur, BA,[2] Kimberly Curseen, MD,[3] Dio Kavalieratos, PhD,[4,5] Meredith Maxwell, MD,[3] Tammie Quest, MD,[3] and Ali John Zarrabi, MD[3]

Abstract

Introduction: Our academic ambulatory palliative care program has counseled, monitored, and certified patients for cannabis as part of routine palliative care practice for six years.
Objective: We describe the population certified for cannabis and policies, procedures, and medicolegal challenges in our palliative care clinic.
Methods: We performed a retrospective review of patients, qualifying diagnoses for cannabis certification, reasons for referral, and number of annual certifications.
Results: Between 2015 and 2021, we certified 1711 patients for cannabis. The most common indications were cancer (64%), pain (24%), and neuropathy (9%). Other three months in 2021, 28% of new referrals to our practice were certified for cannabis and 15% of patients were referred explicitly for cannabis certification.
Conclusion: Despite legal and practical challenges to implementing a medical cannabis program, our palliative care program has fully integrated cannabis as part of our standard outpatient clinical practice.

Cannabis in Palliative Care: A Systematic Review of Current Evidence

Marjan Doppen, MCSc, Stacey Kung, PhD, Ingrid Maijers, MSc, Mary John, MBChB, Harriette Dunphy, MBChB, Hermaleigh Townsley, MBChB, BMedSc(Hons), Allie Eathorne, Bsc, Alex Semprini, PhD, and Irene Braithwaite, PhD, MD

Context. Palliative care aims to improve the quality of life in patients with incurable illness. Medicinal cannabis (MC) has been used in the palliative care setting to address multiple symptoms in patients.

Objectives. To evaluate the full scope of available literature investigating the effects and potential harms of MC on symptom management and quality of life in palliative care.

Methods. PubMed, Embase, The Cochrane Library and clinicaltrials.gov were searched for eligible articles, published between 1960 and September 9, 2021. Quality of the evidence was assessed in accordance with Grading of Recommendations, Assessment, Development and Evaluations. Risk of bias was assessed using the RoB 2 tool for randomised controlled trials and the Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) tool for non-randomized trials.

Results. Fifty-two studies (20 randomised; 32 non-randomised) with 4786 participants diagnosed with cancer (n = 4491), dementia (n = 43), AIDS (n = 235), spasticity (n = 16), NORSE syndrome (n = 1) were included. The quality of evidence was 'very low' or 'low' for all studies, and low for only two randomised controlled trials. Positive treatment effects (statistical significance with $P < 0.05$) were seen for some MC products in pain, nausea and vomiting, appetite, sleep, fatigue, chemosensory perception and paraneoplastic night sweats in patients with cancer, appetite and agitation in patients with dementia and appetite, nausea and vomiting in patients with AIDS. Meta-analysis was unable to be performed due to the wide range of cannabis products used and the heterogeneity of the study outcomes.

Conclusion. While positive treatment effects have been reported for some MC products in the palliative care setting, further high quality evidence is needed to support recommendations for its use in clinical practice. J Pain Symptom Manage 2022;64: e260–e284.

Cannabinoids for behavioral symptoms in severe dementia: Safety and feasibility in a long-term pilot observational study in nineteen patients

Sophie Pautex[1,2†], Federica Bianchi[1,3*†], Youssef Daali[2,4,5], Marc Augsburger[6,7], Christian de Saussure[3], James Wampfler[3], François Curtin[2,4], Jules Desmeules[2,4,5‡] and Barbara Broers[2,8‡]

Front. Aging Neurosci. 14:957665.
doi: 10.3389/fnagi.2022.957665

- N=19
- Offen, unkontrolliert
- Behandlungsdauer: bis zu 13 Monate
- Mittleres Alter = 81,4 Jahre
- Mittlere Dosis: 12,4 mg THC/24,8 mg CBD

TABLE 1 Baseline characteristics.

Residents (*n*)		19
Sex (*n*; %)		
Male		2 (10.5%)
Female		17 (89.5%)
Characteristics (Mean ± SD; Range)		
Age, years		81.4 ± 7.7; 61–95
Weight, kg		61.7 ± 8.6; 50.5–76.5
Blood pressure, mmHg	Systolic	129.2 ± 17.5; 105.0–160.0
	Diastolic	70.0 ± 6.5; 60.0–80.0
MMS		1,4 ± 2.4; 0–9
Diagnosis of dementia (*n*; %)		
Alzheimer's disease		11 (57.9%)
Vascular		4 (26.3%)
Parkinson's disease		1 (5.3%)
Unspecified		2 (10.5%)
Comorbidities (*n*; %)		
Neurological system disease (of which epilepsy)		4 (26.3%) [3 (15.8%)]
Cardiovascular disease		3 (15.8%)
Gastrointestinal disease		2 (10.5%)
Urogenital system disease		2 (10.5%)
Psychiatric disease		1 (5.3%)
Respiratory system disease		1 (5.3%)
Others (including locomotor and endocrine system disease)		8 (42.1%)
Concomitant medications (Mean ± SD; Range)		
Psychotropics, analgesics, diuretics, laxatives, cardiovascular system treatments		7 ± 2; 3–11

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Deutliche Verbesserung von

- “neuropsychiatric problems”
- “Agitation”
- “Rigidity”
- “Most invalidating daily activity”
- “Disabling behavior trouble scores”

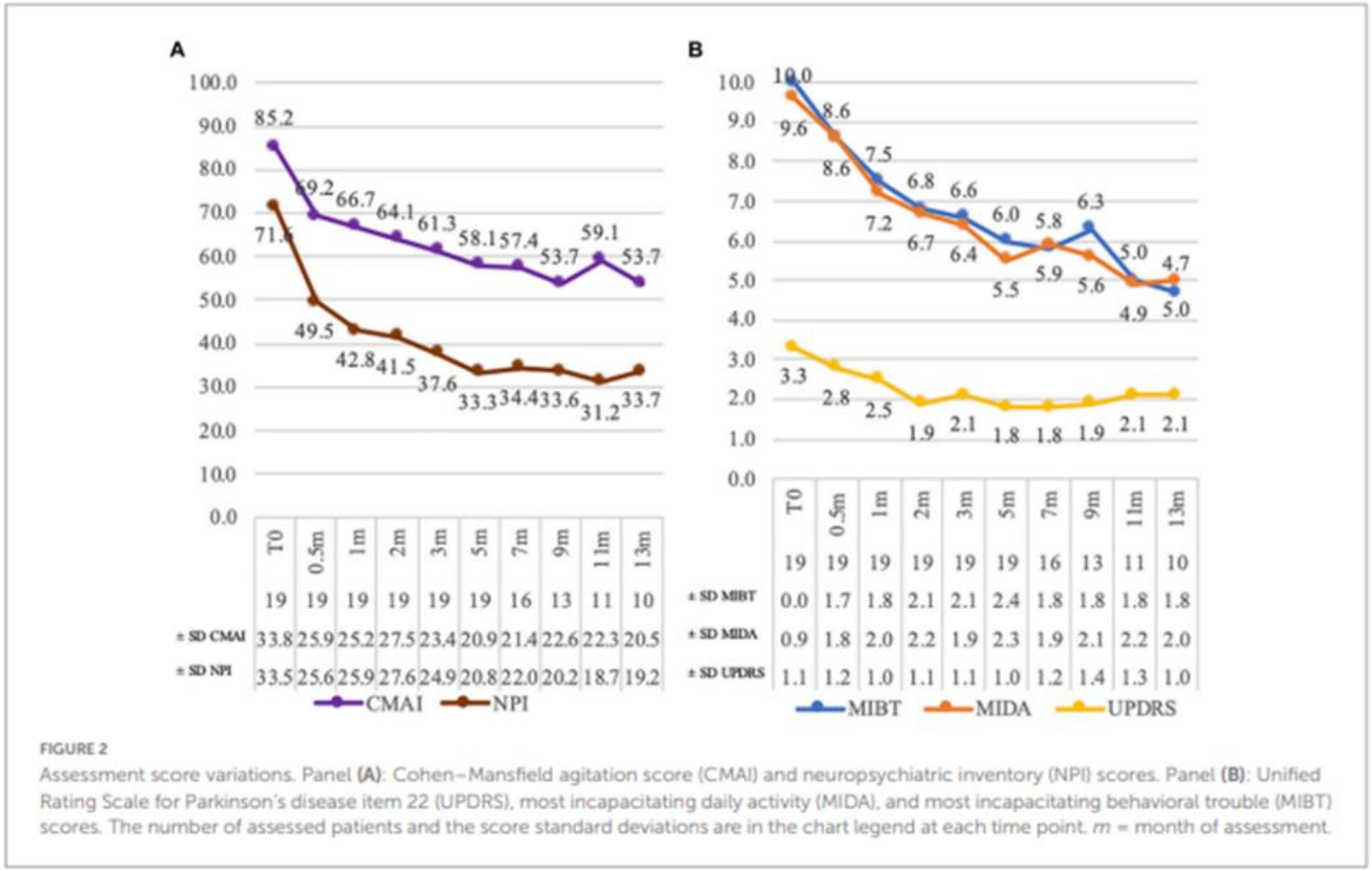

FIGURE 2
Assessment score variations. Panel **(A)**: Cohen–Mansfield agitation score (CMAI) and neuropsychiatric inventory (NPI) scores. Panel **(B)**: Unified Rating Scale for Parkinson's disease item 22 (UPDRS), most incapacitating daily activity (MIDA), and most incapacitating behavioral trouble (MIBT) scores. The number of assessed patients and the score standard deviations are in the chart legend at each time point. *m* = month of assessment.

Cannabis THC/CBD 1:2 gegen Schmerzen bei Demenz

Medical cannabinoids for painful symptoms in patients with severe dementia: a randomized, double-blind cross-over placebo-controlled trial protocol

Federica Bianchi[1,2*], Sophie Pautex[2,3], James Wampfler[1], François Curtin[3,4], Youssef Daali[3,4,5], Jules Alexandre Desmeules[3,5] and Barbara Broers[3,6]

Front. Pain Res. 4:1108832.
doi: 10.3389/fpain.2023.1108832

TABLE 1 Study drug titration.

Day	Number of drops in the morning	Number of drops in the evening	Total drops in the day (mg THC/mg CBD)
1	0	7	7 (2.5 mg THC/5 mg CBD)
2	0	7	7 (2.5 mg THC/5 mg CBD)
3	7	7	14 (5 mg THC/10 mg CBD)
4	7	7	14 (5 mg THC/10 mg CBD)
5	7	14	21 (7.5 mg THC/15 mg CBD)
6	7	14	21 (7.5 mg THC/15 mg CBD)
7	14	14	28 (10 mg THC/20 mg CBD)
8	14	14	28 (10 mg THC/20 mg CBD)
9	14	21	35 (12.5 mg THC/25 mg CBD)
10	14	21	35 (12.5 mg THC/25 mg CBD)
11	21	21	42 (15 mg THC/30 mg CBD)
12	21	21	42 (15 mg THC/30 mg CBD)
13	21	28	49 (17.5 mg THC/35 mg CBD)
14	21	28	49 (17.5 mg THC/35 mg CBD)
15	28	28	56 (20 mg THC/40 mg CBD)

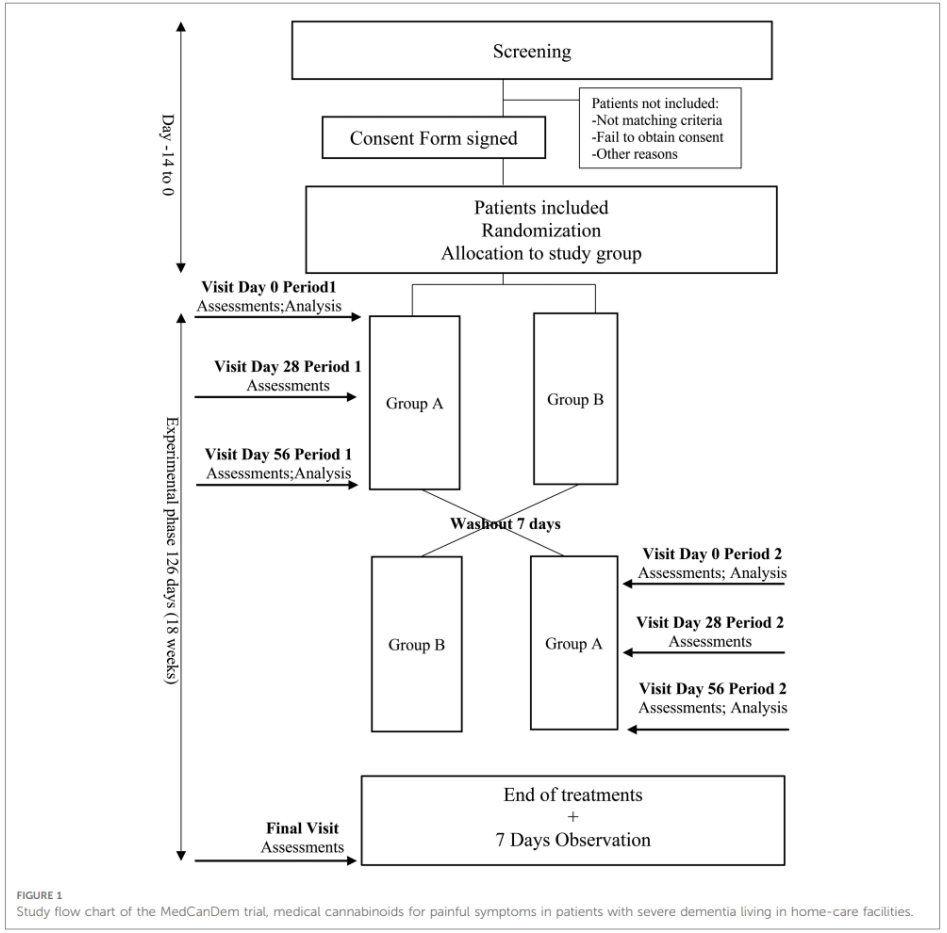

FIGURE 1
Study flow chart of the MedCanDem trial, medical cannabinoids for painful symptoms in patients with severe dementia living in home-care facilities.

Materials and methods: Participants will be patients suffering from severe dementia associated with pain and behavioral troubles and living in long-term care facilities. We selected five facilities specialized in caring for severely demented patients in Geneva (Switzerland). A total of 24 subjects will be randomized 1:1 to the sequence study intervention/placebo or the sequence placebo/study intervention. Patients will receive study intervention treatment or placebo for eight weeks, and then after a one-week wash-out, treatments will be inversed for another eight weeks. The intervention will be a standardized THC/CBD 1:2 oil extract, and the placebo will be a hemp seed oil. The primary

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6	7	14	21 (7.5 mg THC/15 mg CBD)
7	14	14	28 (10 mg THC/20 mg CBD)
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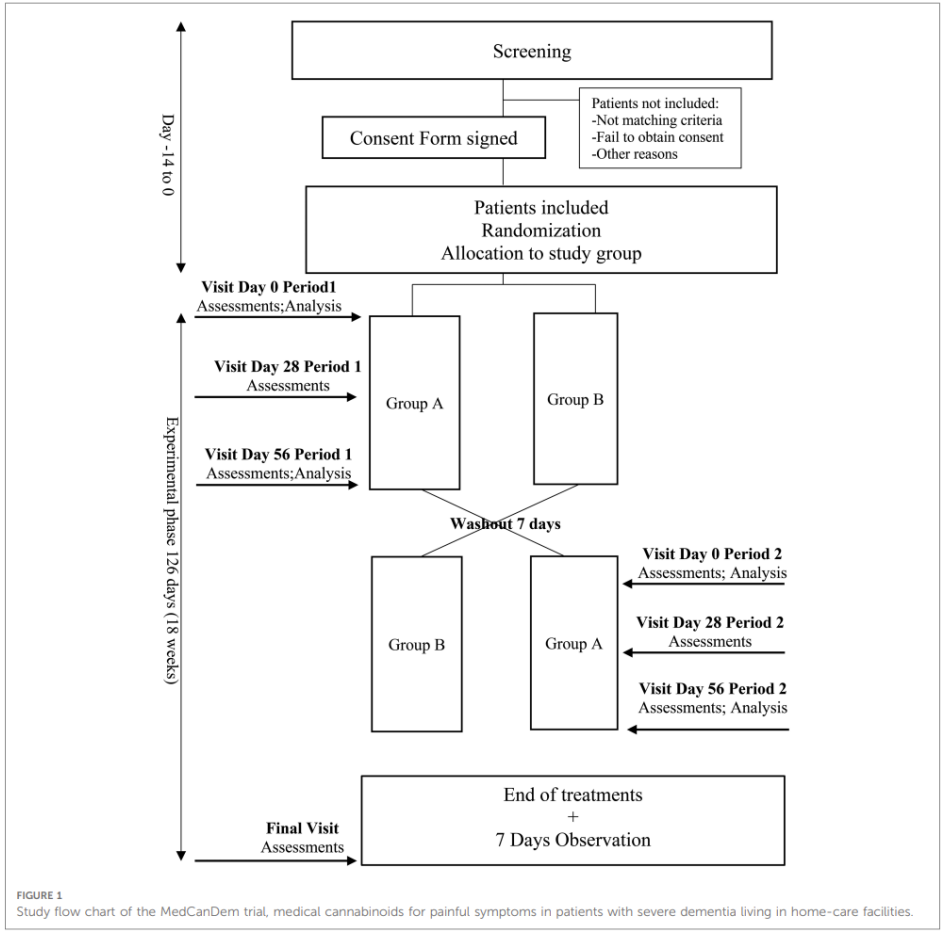

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Review

Understanding the Modulatory Effects of Cannabidiol on Alzheimer's Disease

Alzheimer's Disease. *Brain Sci.* **2021**, *11*, 1211. https://doi.org/10.3390/brainsci11091211

Yinyi Xiong [1,2] and Chae-Seok Lim [1,*]

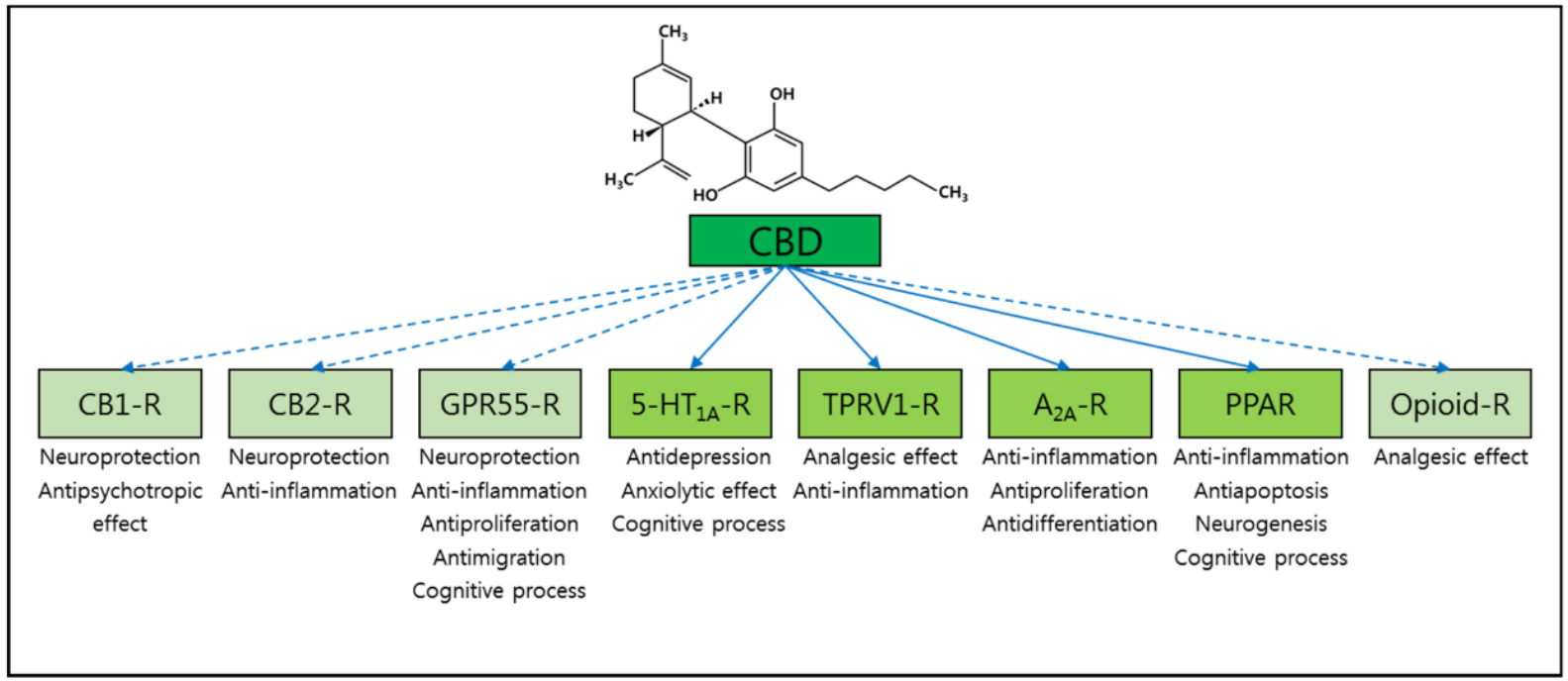

Figure 3. Potential biological targets of CBD in AD treatment. Based on the property of each potential receptor target of CBD and well-known mechanism studies of CBD-mediated therapeutic functions, several potential biological targets of CBD involved in AD treatment have been proposed, including CB1, CB2, GPR55, 5-HT_{1A}, TPRV1, A_{2A}, PPARs, and opioid receptors. Black arrows indicate receptors activated by CBD, whereas dotted arrows indicate receptors inhibited by CBD. The therapeutic roles of CBD mediated by each receptor are listed underneath to provide insights for CBD application in AD treatment.

Review

Understanding the Modulatory Effects of Cannabidiol on Alzheimer's Disease

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Yinyi Xiong [1,2] and Chae-Seok Lim [1,*]

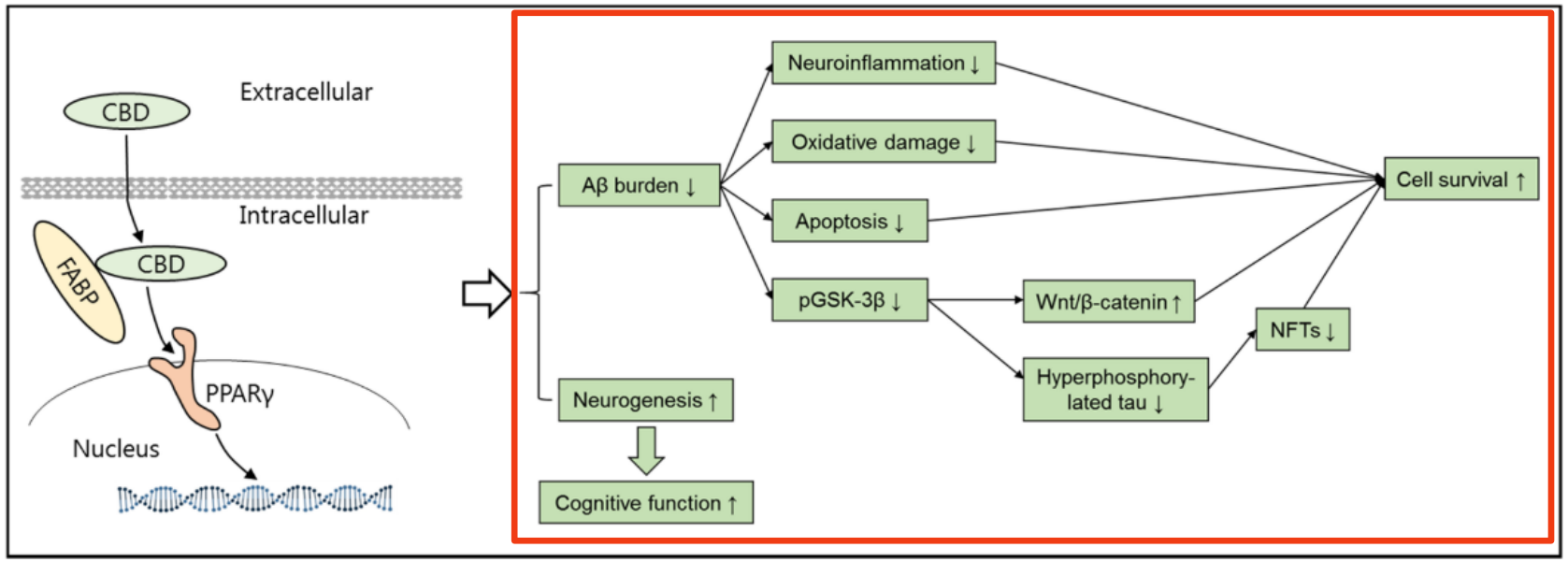
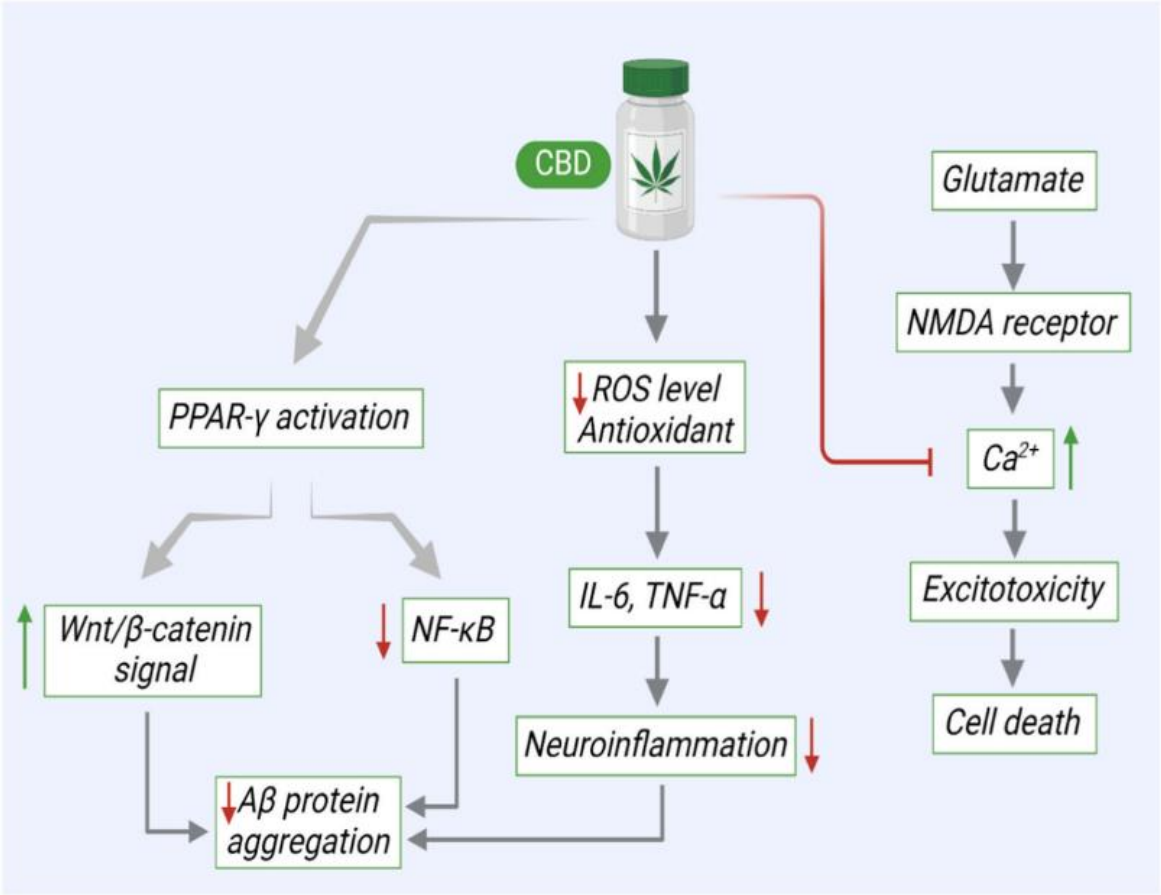


Figure 4. Summary of the main findings illustrating the neuroprotective functions of CBD against AD pathology. CBD can be translocated into the nucleus by FABPs and activate nuclear PPARγ to induce gene expression, resulting in a series of improvements against Aβ-induced aberrant changes in AD, such as reduced neuroinflammation, oxidative changes, and apoptosis. In addition, CBD can contribute to the inhibition of hyperphosphorelated tau and activation of Wnt/β-catenin signaling by recovering Aβ-induced pGSK-3β. Finally, the CBD-mediated therapeutic changes facilitate neuronal survival. In addition, CBD enhances neurogenesis in AD. Overall, both CBD-mediated neuroprotection against Aβ-induced pathologies and CBD-mediated increase in neurogenesis might contribute to the improved cognitive function observed in AD.

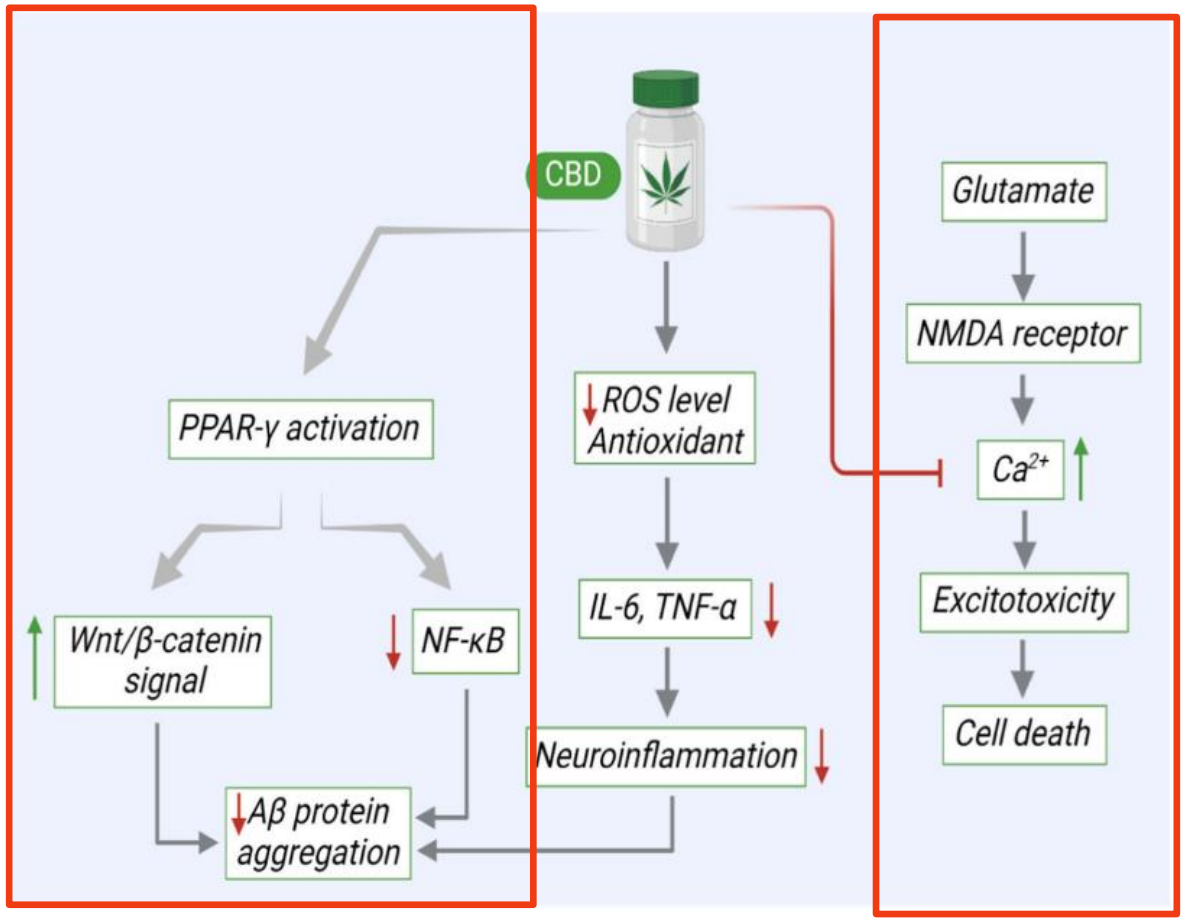
Wirkungsmechanismen von CBD bei Alzheimer-Demenz



- CBD hat neuroprotektive Wirkungen durch
  - Aktivierung des PPAR-ɣ-Rezeptors
    - Dadurch Wnt/β-Catenin-Wirkung verstärkt
    - Dadurch hemmende Wirkung von NF-κB verstärkt
  - Dadurch Verminderung von Entzündung und β-Amyloid-Protein-Aggregation im Gehirn
- CBD vermindert ROS-Produktion (freie Radikale)
  - Dadurch reduzierte Produktion von Entzündungsmarkern wie TNF-α und IL-6 in Gliazellen
  - Dadurch verminderte Neuroinflammation
- CBD interagiert mit NMDA-Rezeptoren
  - Dadurch verminderte Ca2+-Überladung
  - Dadurch reduzierte neuronale Erregung
  - Dadurch verminderte neuronale Schädigung

Jha SK, Nelson VK, Suryadevara PR, Panda SP, Pullaiah CP, Nuli MV, Kamal M, Imran M, Ausali S, Abomughaid MM, Srivastava R, Deka R, Pritam P, Gupta N, Shyam H, Singh IK, Pandey BW, Dewanjee S, Jha NK, Jafari SM. Cannabidiol and neurodegeneration: From molecular mechanisms to clinical benefits. Ageing Res Rev. 2024 Sep;100:102386. doi: 10.1016/j.arr.2024.102386. Epub 2024 Jul 4. PMID: 38969143.

Wirkungsmechanismen von CBD bei Alzheimer-Demenz



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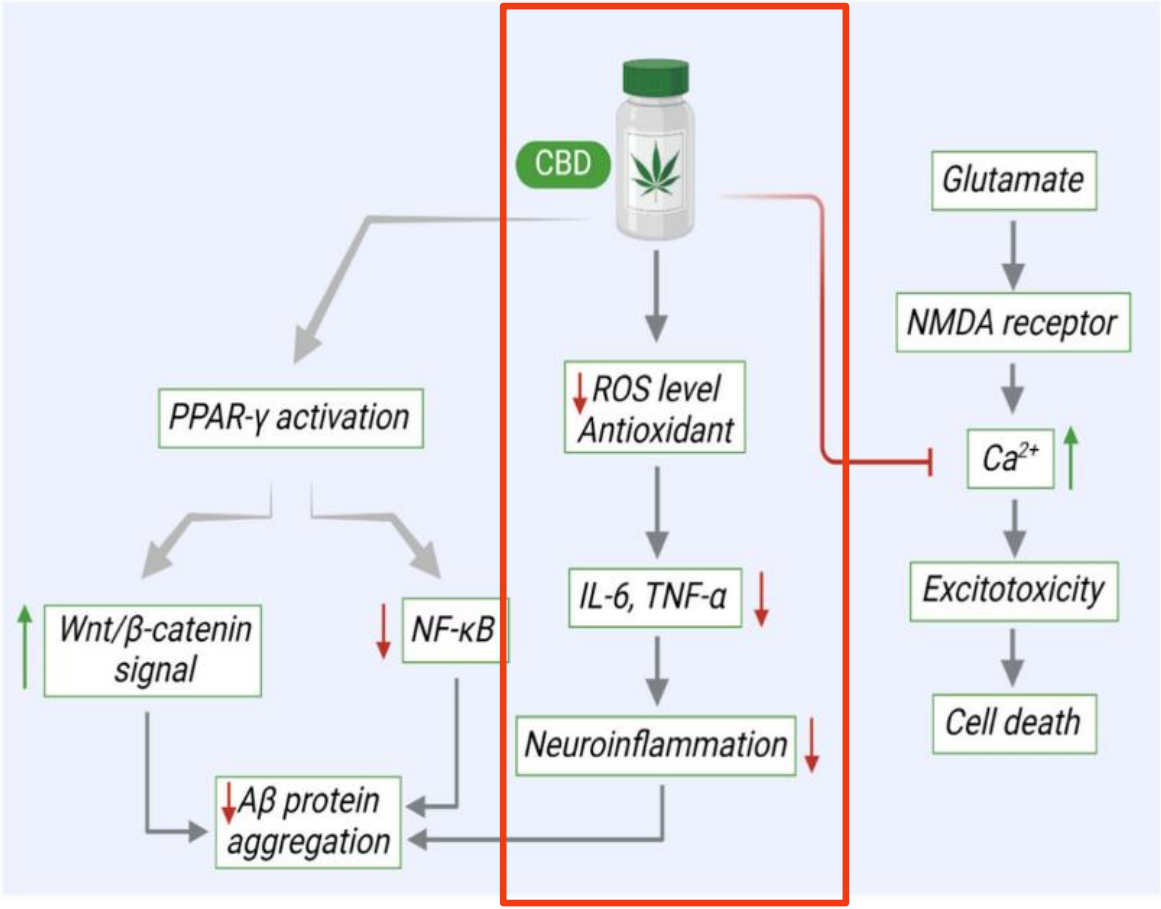
  - Dadurch verminderte neuronale Schädigung

Jha SK, Nelson VK, Suryadevara PR, Panda SP, Pullaiah CP, Nuli MV, Kamal M, Imran M, Ausali S, Abomughaid MM, Srivastava R, Deka R, Pritam P, Gupta N, Shyam H, Singh IK, Pandey BW, Dewanjee S, Jha NK, Jafari SM. Cannabidiol and neurodegeneration: From molecular mechanisms to clinical benefits. Ageing Res Rev. 2024 Sep;100:102386. doi: 10.1016/j.arr.2024.102386. Epub 2024 Jul 4. PMID: 38969143.

Wirkungsmechanismen von CBD bei Alzheimer-Demenz



- CBD hat neuroprotektive Wirkungen durch
  - Aktivierung des PPAR-ɣ-Rezeptors
    - Dadurch Wnt/β-Catenin-Wirkung verstärkt
    - Dadurch hemmende Wirkung von NF-κB verstärkt
  - Dadurch Verminderung von Entzündung und β-Amyloid-Protein-Aggregation im Gehirn
- CBD vermindert ROS-Produktion (freie Radikale)
  - Dadurch reduzierte Produktion von Entzündungsmarkern wie TNF-α und IL-6 in Gliazellen
  - Dadurch verminderte Neuroinflammation
- CBD interagiert mit NMDA-Rezeptoren
  - Dadurch verminderte Ca2+-Überladung
  - Dadurch reduzierte neuronale Erregung
  - Dadurch verminderte neuronale Schädigung

Jha SK, Nelson VK, Suryadevara PR, Panda SP, Pullaiah CP, Nuli MV, Kamal M, Imran M, Ausali S, Abomughaid MM, Srivastava R, Deka R, Pritam P, Gupta N, Shyam H, Singh IK, Pandey BW, Dewanjee S, Jha NK, Jafari SM. Cannabidiol and neurodegeneration: From molecular mechanisms to clinical benefits. Ageing Res Rev. 2024 Sep;100:102386. doi: 10.1016/j.arr.2024.102386. Epub 2024 Jul 4. PMID: 38969143.

Alzheimer-Erkrankung durch Entzündung bedingt?

The Effect of Chronic Inflammation and Oxidative Stress on Alzheimer's Disease Progression: A Systematic Review

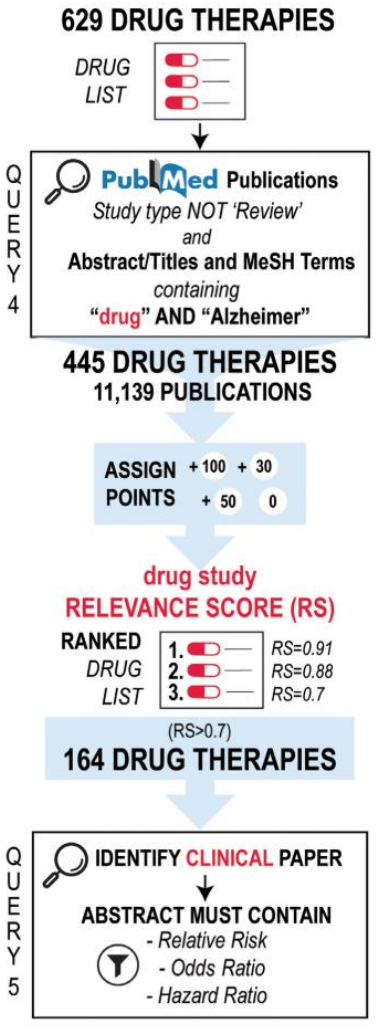
Elisa A. Bornemann [1], Hari Krishna Kamma [2], Mohammad Alabbas [3], Mohammad Elashahab [4], Naushad Abid [5], Sara Manaye [6], Kaaviya Cheran [7], Chinmayee Murthy [8], Sheiniz Giva [9], Sai Sri Penumetcha [7, 10]

Cureus 17(5): e84057. DOI 10.7759/cureus.84057

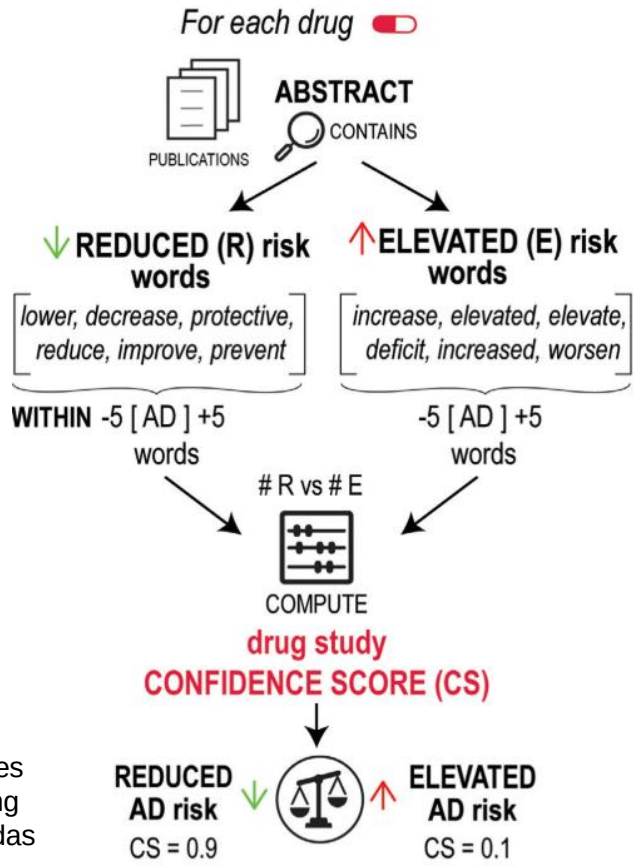
Abstract

Alzheimer's Disease (AD) is known to be the most common type of dementia among older adults. It is characterized by a gradual decline in cognitive abilities, particularly the deterioration of short-term memory. The hallmark neuropathology of AD is the accumulation of neurofibrillary tau tangles (NFTs), which consist of hyperphosphorylated tau protein, as well as extracellular beta-amyloid plaques in the brain. Evidence suggests that AD is not solely tied to neurological mechanisms, and that other factors, such as inflammation, can affect disease progression, including systemic inflammation seen in metabolic syndrome and oxidative stress. We performed a literature review by searching databases and conducting a manual search of studies regarding the relationship between AD, inflammation, and oxidative stress, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. After meticulous scrutiny and the application of inclusion and exclusion criteria to clinically relevant papers, 14 studies were deemed relevant for this review regarding the effect of inflammation and oxidative stress in relation to AD and its progression. The findings conclude that there is new evidence supporting the theory that chronic inflammation plays a significant role in the progression of the disease, which could allow for future advancements in treatments, diagnostics, and preventive tools for its management. These advancements could include the implementation and use of biomarkers for inflammation, the use of algorithms to stratify the disease's grade, and the use of mineral supplements like zinc. Furthermore, the management of underlying conditions has been shown to be beneficial in slowing the progression of AD.

Entzündungshemmer wirksam bei Alzheimer-Erkrankung?



Analyse der Wirkungen von Arzneimitteln auf die Alzheimer-Krankheit Berechnung des Relevanz-Scores (RS) und Identifizierung von klinischen Studien



Berechnung des Vertrauens-Scores (CS) zur Bewertung und Einstufung der therapeutischen Wirkung auf das Alzheimer-Risiko

Vitali F, Branigan GL, Brinton RD. Preventing Alzheimer's disease within reach by 2025: Targeted-risk-AD-prevention (TRAP) strategy. Alzheimers Dement (N Y). 2021 Sep 20;7(1):e12190. doi: 10.1002/trc2.12190. PMID: 34584937; PMCID: PMC8451031.

Entzündungshemmer wirksam bei Alzheimer-Erkrankung?

TABLE 2 Drugs supported by clinical studies resulting from TRAP pipeline

Drug name	# Total reports*	# Reports included in stats†	# Positive reports	# Negative reports	CS	RS	Drug category
Pioglitazone	115	11	11	0	0.923	1	Metabolic
Ibuprofen	180	18	17	1	0.900	1	Anti-inflammatory
Indomethacin	118	8	8	0	0.900	1	Anti-inflammatory
Atorvastatin	101	15	14	1	0.882	1	Statin
Pravastatin	41	6	6	0	0.875	1	Statin
Simvastatin	140	19	17	2	0.857	1	Statin
Estradiol	509	80	65	15	0.805	1	Hormone
Celecoxib	82	8	7	1	0.800	1	Anti-inflammatory
Rosuvastatin	18	3	3	0	0.800	0.995	Statin
Lisinopril	9	3	3	0	0.800	0.987	Cardiac
Vitamin A	73	17	14	3	0.789	1	Other
Valproic acid	83	12	10	2	0.786	1	Psychiatric
Naproxen	77	12	10	2	0.786	1	Anti-inflammatory
Diclofenac	27	6	5	1	0.750	1	Anti-inflammatory
Metformin	146	13	10	3	0.733	1	Metabolic
Testosterone	260	39	29	10	0.732	1	Hormone

*Total number of publications including the drug of interest and the word *"Alzheimer."*
†Total number of publications including words associated with reduced risk of AD.
CS, confidence score; RS, relevance score.

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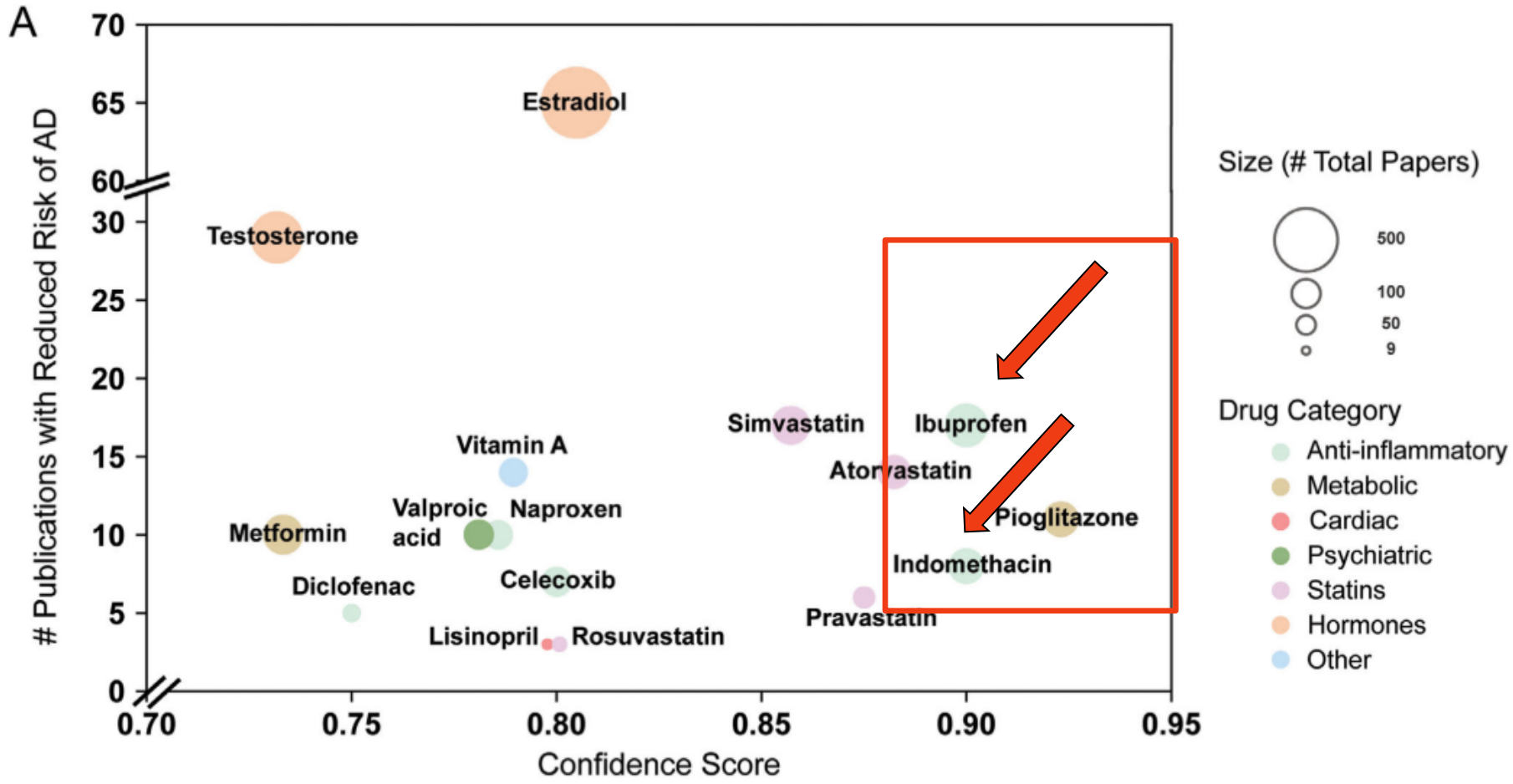

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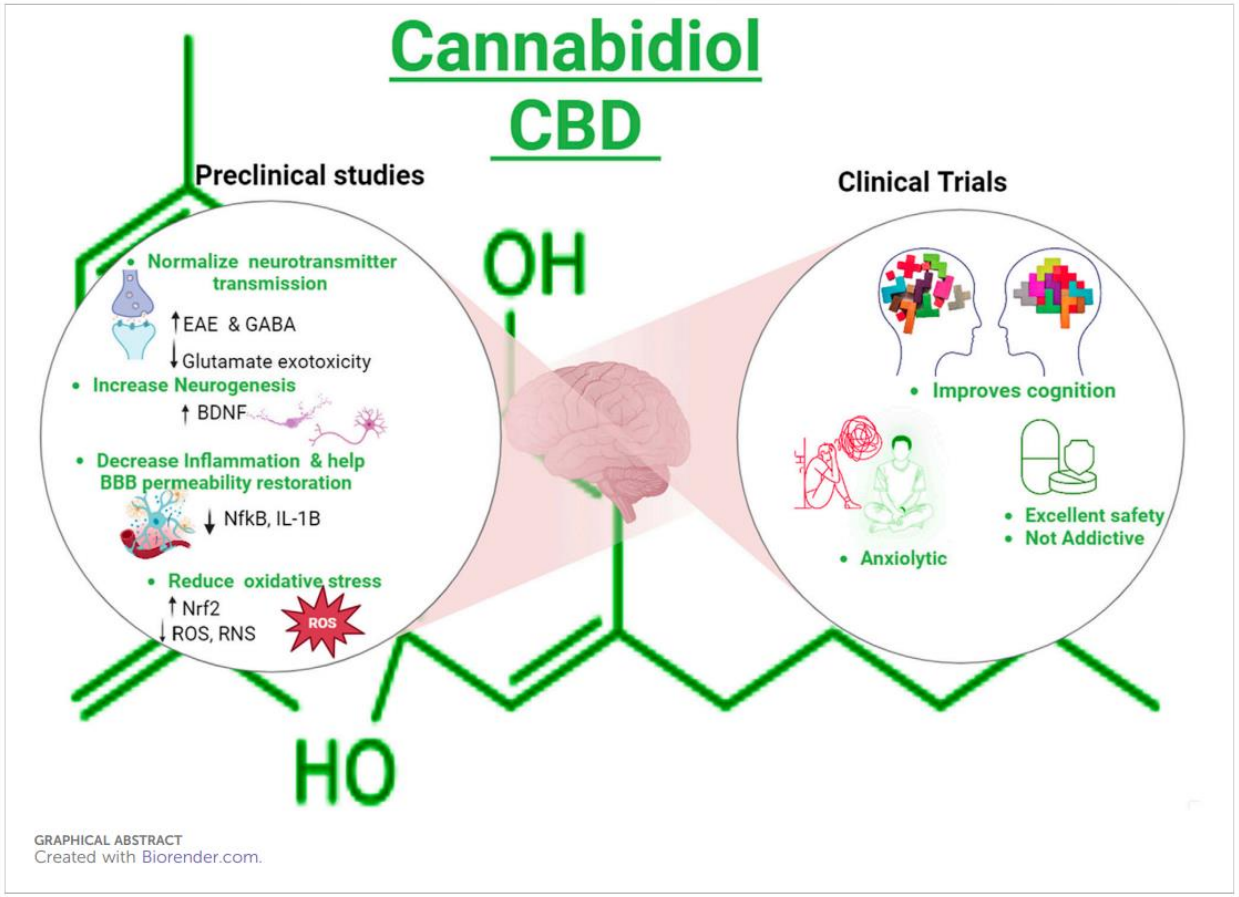
CBD zur Behandlung der leichten kognitiven Beeinträchtigung (mild cognitive impairment, MCI)



Übersichtsarbeit:

- CBD verbesserte in 9/16 analysierten Studien Ängste und kognitive Beeinträchtigungen
- Orale Einzeldosen: 200mg - 1.500 mg
- Gut verträglich
- Keine Abhängigkeit
- CBD potenziell wirksam bei Alzheimer-Krankheit
- CBD ein vielversprechender Kandidat für die Behandlung neurokognitiver Störungen

Yndart Arias A, Vadell K, Vashist A, Kolishetti N, Lakshmana MK, Nair M, Liuzzi JP. Cannabidiol, a plant-derived compound, is an emerging strategy for treating cognitive impairments: comprehensive review of randomized trials. Front Pharmacol. 2024 Sep 11;15:1403147. doi: 10.3389/fphar.2024.1403147. PMID: 39323633; PMCID: PMC11422111.

Cannabis and Cannabinoid Research
Volume 8, Number 2, 2023

DOI: 10.1089/can.2021.0209

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ORIGINAL RESEARCH

Cannabidiol as a Treatment for Neurobiological, Behavioral, and Psychological Symptoms in Early-Stage Dementia: A Double-Blind, Placebo-Controlled Clinical Trial Protocol

Jessica G. Bartschi,[1–3,*] Lisa-Marie Greenwood,[3,4] Amy Montgomery,[2,5] Lon Dortants,[1,3] Katrina Weston-Green,[2,3,6] Xu-Feng Huang,[2,3,6] Nagesh Pai,[2,6,7] Jan Potter,[2,6,7] Mark M. Schira,[1] Rodney Croft,[1,2] and Nadia Solowij[1–3]

Abstract

Rationale: The slowing of disease progression in dementia in the early stages of diagnosis is paramount to improving the quality of life for those diagnosed and their support networks. Accumulating evidence suggests that CBD, a constituent of *Cannabis sativa*, is associated with neuroprotective, neuroendocrine, and psychotherapeutic effects, suggesting that it may be beneficial to dementia treatment. However, no published human study to date has examined this possibility. This trial aims to determine whether daily treatment with CBD over a 12-week period is associated with improved neurobiological, behavioral, and psychological outcomes in individuals living with early-stage dementia.

Methods: Sixty participants with early-stage dementia will be recruited for a randomized, double-blind, placebo-controlled clinical trial. Participants will be randomized into either 99.9% pure CBD or placebo treatment conditions and administered two capsules per day for 12 weeks. Participants will commence a 200 mg/day dose for 2 weeks before escalating to 300 mg/day for the remaining 10 weeks. Neuroimaging and blood-based neuroendocrine profiles will be assessed at baseline and post-treatment. Psychological and behavioral symptoms will be assessed at baseline, 6 weeks, and post-treatment. Monitoring of health and side-effects will be conducted through weekly home visits.

Discussion: This study is among the first to investigate the effects of isolated CBD in improving neuroanatomical and neuroendocrine changes, alongside psychological symptoms, during the early stages of dementia diagnosis. The outcomes of this trial have the capacity to inform a potential novel and accessible treatment approach for individuals living with early-stage dementia, and in turn, improve quality of life, prognoses, and treatment outcomes.

Trial Registration: This trial has been registered with the Therapeutic Goods Administration (CT-2020-CTN-03849-1v2) and the Australian and New Zealand Clinical Trials Registry (ACTRN12621001364864).

Keywords: dementia; cannabidiol; clinical trial; brain; neurodegeneration; behavioral and psychological symptoms of dementia (BPSD); hormones

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Geplante Studie: BrainFit-Cannabidiol (BF-CBD)

BrainFit-Cannabidiol (BF-CBD):
Bewertung des Einflusses von oralem Cannabidiol (CBD) auf die Neuroinflammation und Alzheimer-Biomarker in der Rückenmarksflüssigkeit (Liquor) in Kombination mit dem klinischen Verlauf bei Menschen mit leichter kognitiver Beeinträchtigung (mild cognitive impairment, MCI) - eine randomisierte kontrollierte Studie

Studienleiter:innen:

- Prof. Dr. med. Elmar Gräßel, Leiter des Zentrums für Medizinische Versorgungsforschung, Leiter des Bereichs Medizinische Psychologie und Medizinische Soziologie, Psychiatrische Universitätsklinik Erlangen
- Prof. Dr. med. Piotr Lewczuk, Leiter des Labors für Klinische Neurochemie, Psychiatrische Universitätsklinik Erlangen
- Prof. Dr. med. Kirsten R. Müller-Vahl, Oberärztin, Klinik für Psychiatrie, Sozialpsychiatrie und Psychotherapie, Medizinische Hochschule Hannover
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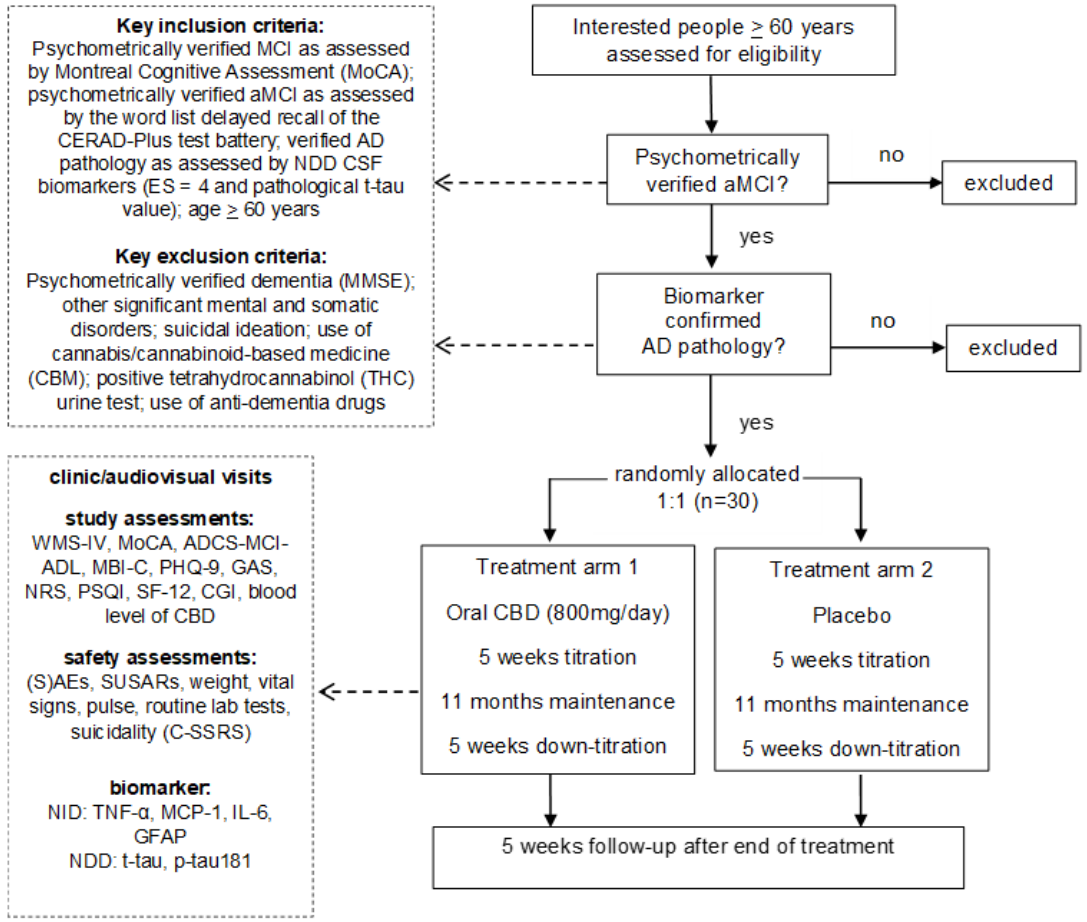

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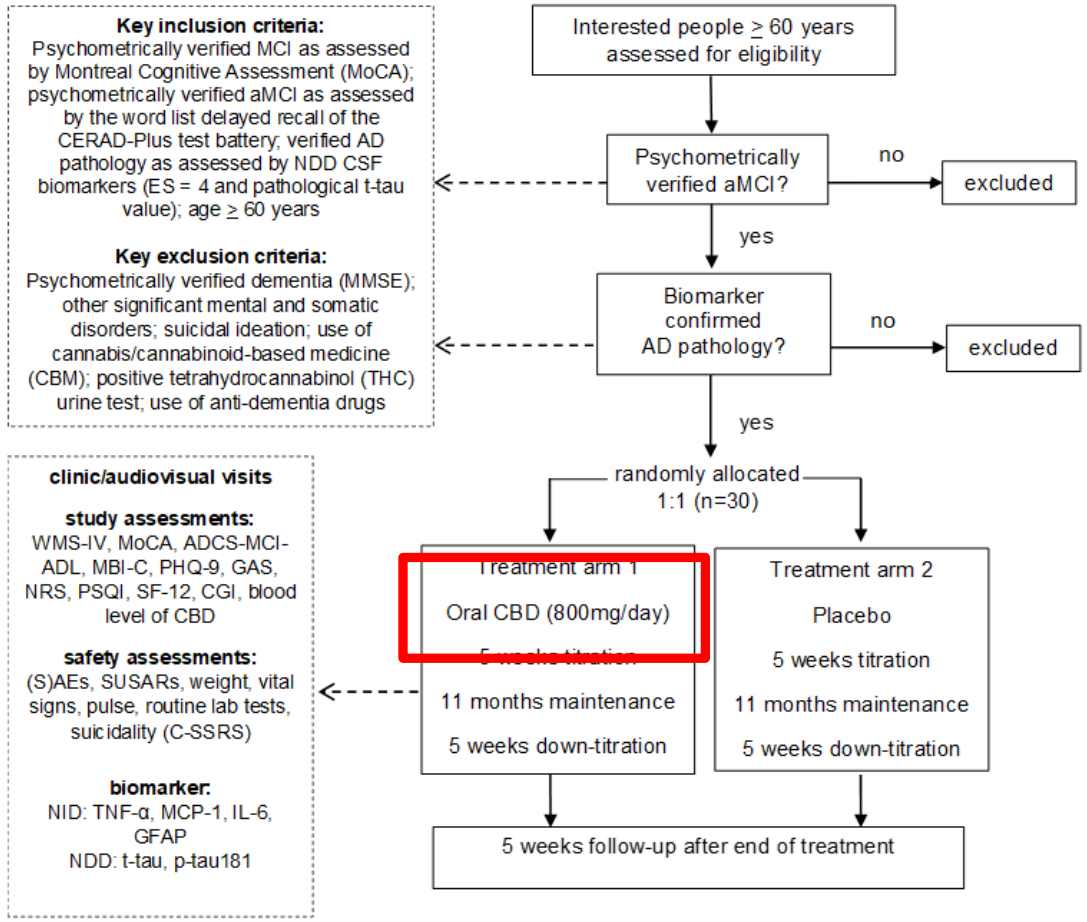

Zusammenfassung

- Cannabis-basierte Medikamente
  - THC
  - CBD
  - THC+CBD
- Zahlreiche Indikationen
- THC-haltige Cannabis-basierte Medikamente mutmaßlich geeignet zur symptomatischen Behandlung von Demenz-Erkrankten
  - Unruhe, Aggressivität, Reizbarkeit, Schlafstörungen, Ängsten, Depression
  - Schmerz, Appetitminderung, Übelkeit
- Hochdosierte CBD-Behandlung hat möglicherweise antiinflammatorische und neuroprotektive Effekte bei Alzheimer-Demenz

Cannabinoide zur Behandlung von Demenz?

Ihre Fragen an Prof. Dr. Kirsten Müller-Vahl

„Sehverlust als Risikofaktor für Demenz“

Termin: **15.07.2025, 11:00 - 11:45 Uhr**

Referent: **Dr. Elzbieta Kuzma**

- Wissenschaftliche Mitarbeiterin im Albertinen Haus - Zentrum für Geriatrie und Gerontologie
- Forschungsschwerpunkt auf Risikofaktoren für Demenz
- Mitherausgeberin des *Journal of Alzheimer's Disease*

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- Heute zum ersten Mal dabei?
  Melden Sie sich für unseren Newsletter an: https://digidem-bayern.de/newsletter/
- digiDEM Bayern auf Social Media

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