

بنام آنکه هستی نام از او یافت
فلک جنبش زمین آرام از او یافت



CANNABIS and KIDNEY

Dr. M TAMADDONDAR
HUMS



نفروتوکسین‌ها و کلیه

Kidney and Nephrotoxins

۱۳-۱۵ مهر ۱۴۰۱-تهران

The nephrologist's guide to cannabis and cannabinoids

- Introduction, Physiology
- Effect on kidney disease



Introduction, Physiology

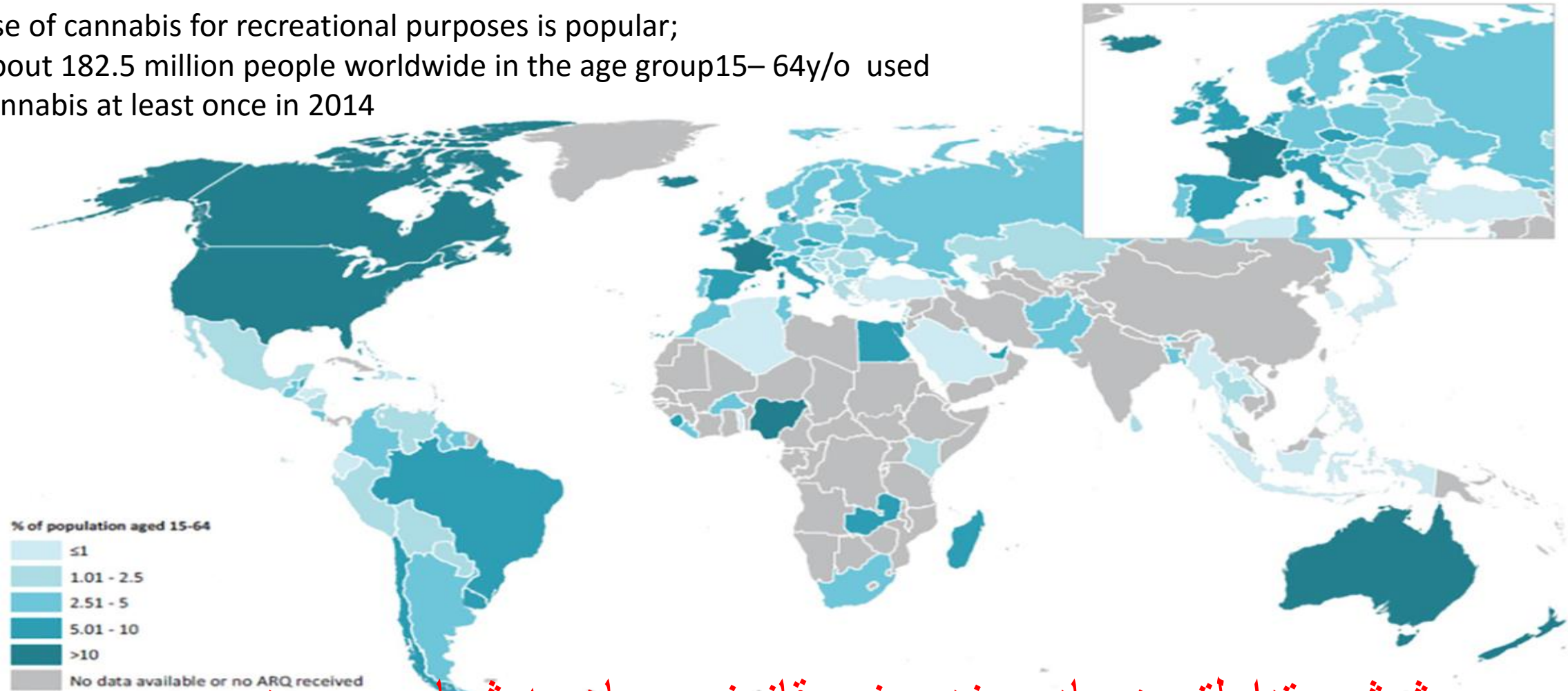


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Use of cannabis for recreational purposes is popular;
About 182.5 million people worldwide in the age group 15–64y/o used cannabis at least once in 2014



Source: UNODC

حشیش متداولترین ماده مخدر غیر قانونی جهان به شمار می‌رود

Fig. 1. Prevalence of cannabis use worldwide in 2014. Modified from United Nations Office on Drugs and Crime, United Nations Office on Drugs and Crime. http://www.unodc.org/wdr2016/field/1.2.2._Prevalence_cannabis.pdf, accessed on March 27, 2017.



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Cannabinoids

EXOCANNABINOIDS

✓ Psychologically active

➤ Tetrahydrocannabinols (THC)

- Cannabinodiol (CBDL),
- Cannabinol (CBN),

✓ No psychological effects

- Cannabigerols (CBGs),
- Cannabichromenes (CBCs),
- Cannabidiols (CBDs)

ENDOCANNABINOIDS

- (AEA), N-arachidonoyl ethanolamide, anandamide
- (2-AG) 2-arachidonoylglycerol



Cannabineae

flowering male plant

seed-bearing female plant,

Activate

Go to Settir



Dark green
Low THC

Light green
High THC

Seeds
Flowers
Leaves
Stems

Cannabis sativa plant

- >480 natural components
- 200 phytocannabinoids, terpenoids, flavonoids
- 66 of them classified as "cannabinoids"

'ENTOURAGE EFFECT'



Cannabis sativa L.

W. Müller

نفروتوکسین ها و کلیه

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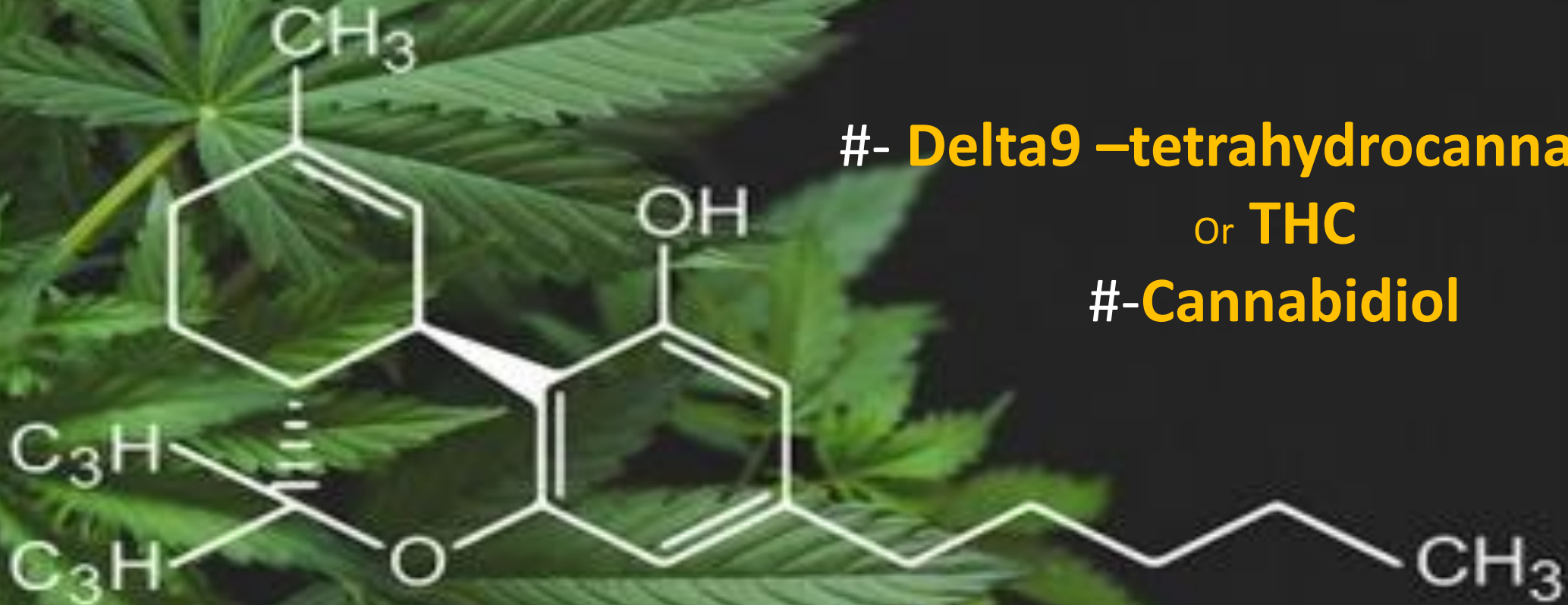


PHYTOCANNABINOIDS

#- **Delta9 –tetrahydrocannabinol**

Or **THC**

#- **Cannabidiol**



THC

بنگ، منگ، گل، علف

آفریقای جنوبی دگا، آفریقای مرکزی کامبا،

ترکیه اسر یا اسرا،

اسپانیا و دیگر کشورها اسامی مختلفی چون، شانگ، چاراز، مکونا

- ✓ Pot, Grass,
- ✓ Weed,
- ✓ Mary Jane
- ✓ Ganja,
- ✓ Marijuana,
- ✓ Smoke,



STRONGER FORMS

‘spice’ or ‘K2’ , XLR-11 Synthetic cannabinoids, potent CB1 agonists
sinsemilla (from female plants)



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Cannabis effects

ACUTE

- relaxation, mild euphoria
- impairment in memory, concentration, judgment
- anxiety, paranoia, psychosis
- Altered sense of time
- Laughing, conjunctival injection and tachycardia

CHRONIC

May not be permanent

- impaired concentration, learning,
- insomnia
- worsening symptoms in schizophrenia

withdrawal syndrome → irritability, insomnia, anorexia, anxiety, and craving.



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Cannabinoids

- > **90%** **INHALATION** onset in minutes, peak 15– 30 min and half-life of 1–2 h
- <**10%** **ORAL** onset to 1–2 h, peak 2–3 h and half-life of 3–6 h

Terminal half-life

- several days in infrequent users
- 1 month in heavy chronic users



Cannabinoids

Highly lipophilic, bioavailability increased with high fat intake.

Metabolism → mostly liver

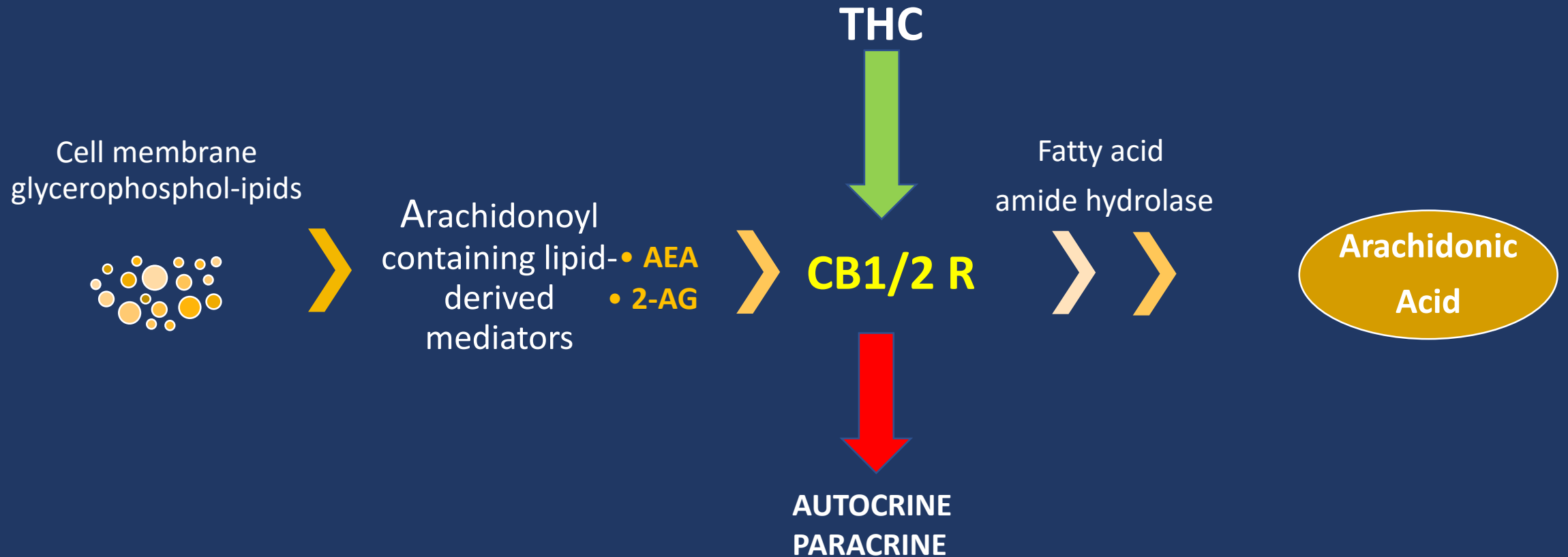
Urine excretion → 20% inactive metabolites

THC has large V_d , high protein binding, slow elimination, non dialyzable

✓ **CBD** is metabolized by CYP3A4 and CYP2C19.



ENDOCANNABINOIDS / EXOCANNABINOIDS



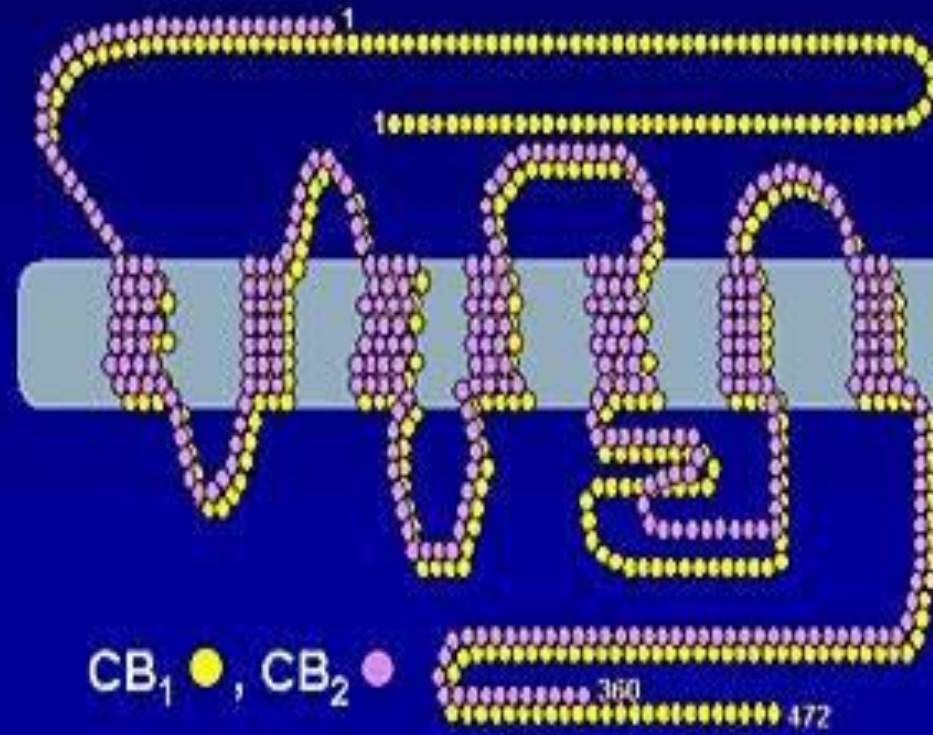
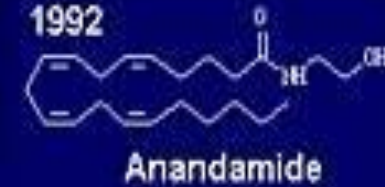
Ubiquitously expressed
Gi/Go-protein-coupled

THC: (psychoactive)
partial agonist CB1R and
CB2R.

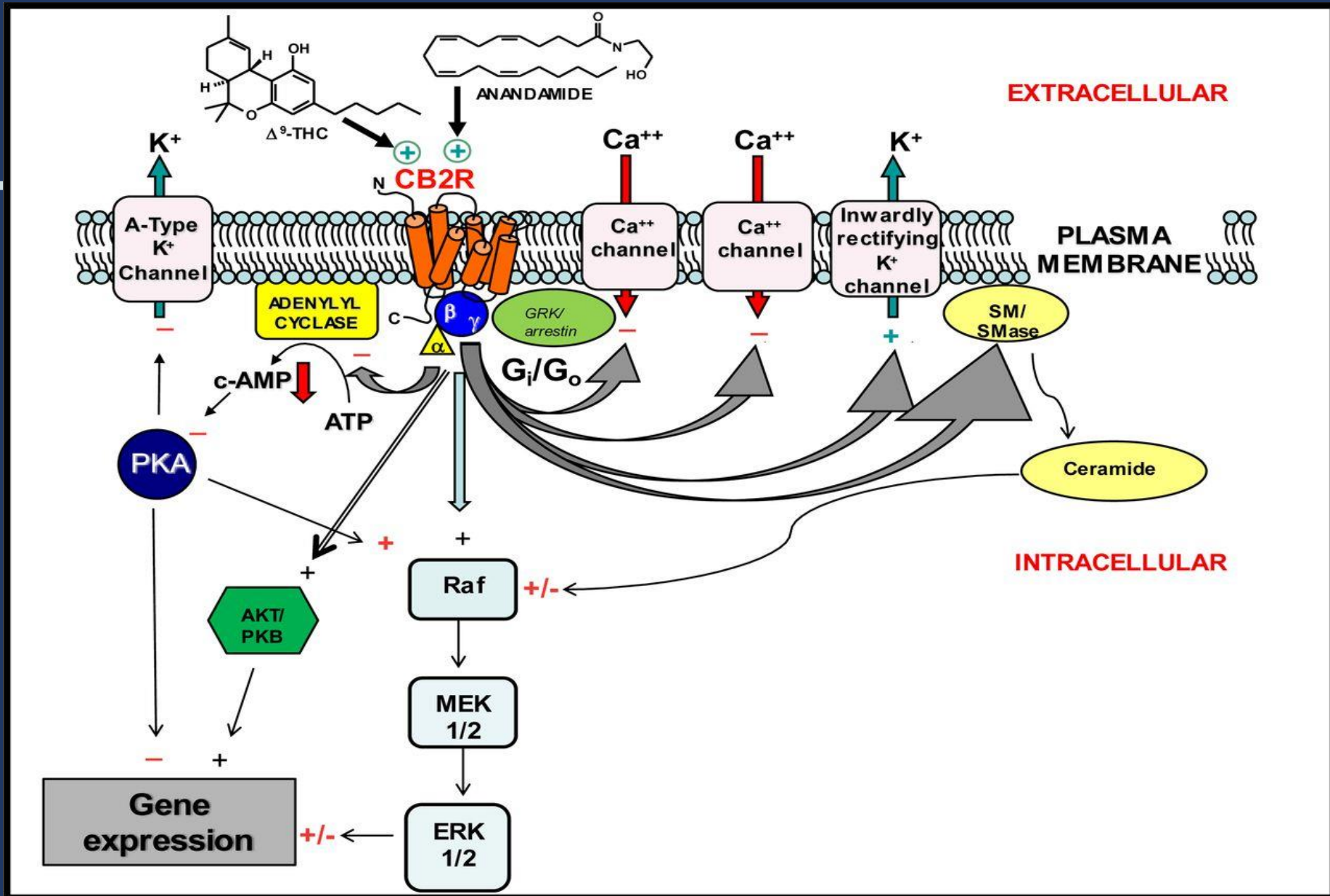
CBD: (little affinity for receptors)
Negative modulator of CB1R
Effects on GPR55, TRPV1, 5-
HT1A, adenosine A2A.

Cannabinoid Receptors

CB1R - CB2R

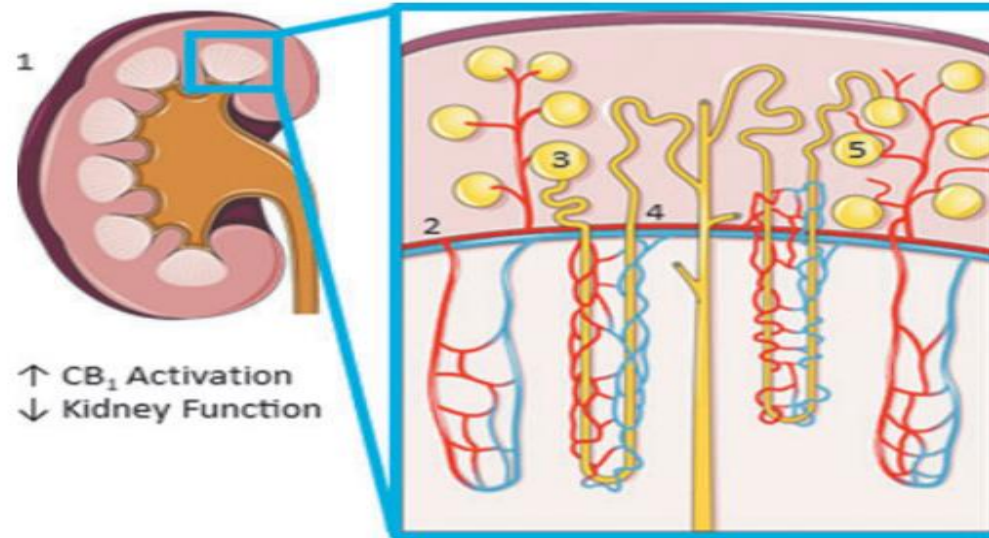


- Hippocampus
- Basal ganglia
- Cortex
- Cerebellum
- Hypothalamus
- Limbic structures
- Brainstem
- Adipocytes
- GI Tract
- Immune cells and tissues



Endocannabinoid System and the Kidneys: From Renal Physiology to Injury and Disease

Janice T. Chua,¹ Donovan A. Argueta,² Nicholas V. DiPatrizio,² Csaba P. Kovesdy,^{3,4} Nosratola D. Vaziri,¹ Kamyar Kalantar-Zadeh,^{1,5} and Hamid Moradi^{1,5,*}



# - Structure	Receptor	Ligand	Physiological Effect	Source
1 – Kidney	CB ₁	AEA	↑ Oxidative & Nitrosative Stress Markers ↑ Apoptosis ↑ Inflammation	35
2 – Juxta-medullary afferent and efferent arterioles	CB ₁	AEA	↑ Vasodilation	17, 31
3 – Glomerular blood vessels	?	AEA	↑ Blood Flow ↓ Filtration Rate	17
4 – Thick ascending Loop of Henle	CB ₁	AEA	↑ NO ₂ Production ↓ Na ⁺ Transport	18
5 – Podocytes and mesangial cells	CB ₁	WIN 55 212-2	↑ Urinary Protein Excretion ↑ VEGF Expression ↓ Nephrin Expression & Levels	40

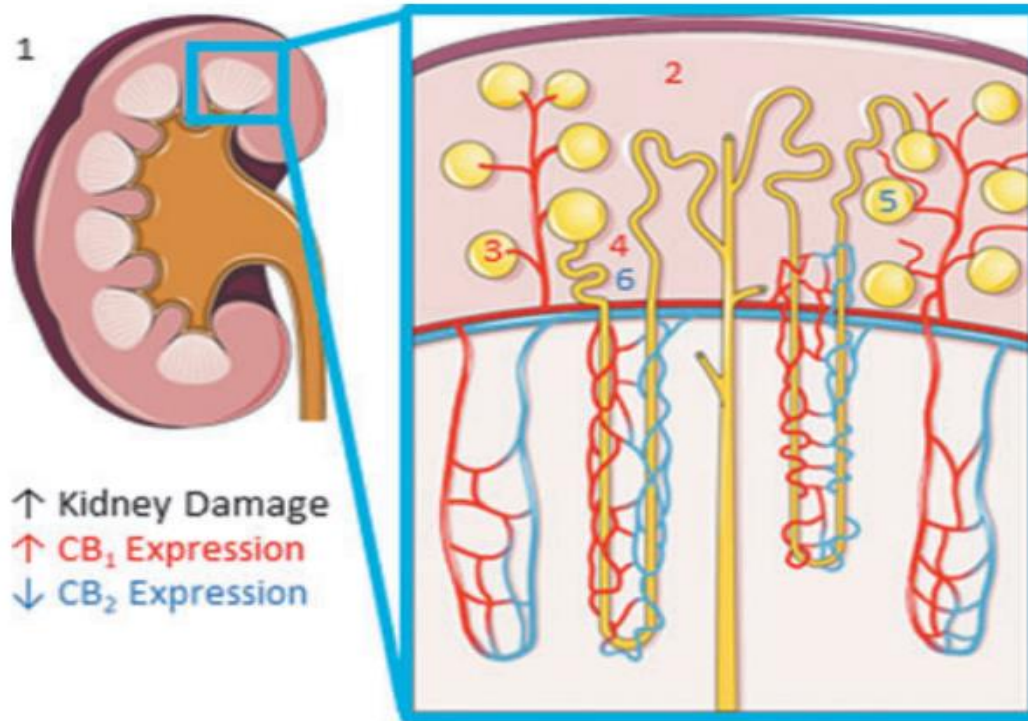
FIG. 1. Roles of the endocannabinoid system in healthy kidney. Images adapted from Servier Medical Art "Kidney" licensed under CC 3.0, https://smart.servier.com/smart_image/kidney

1. Cannabis derived CBD (**Epidiolex**) is an FDA approved pediatric epilepsy
2. The cannabis extract **nabiximols** (**Sativex, THC/CBD 1:1**). MS spasticity symptoms.

Chemotherapy induced nausea FDA approved

1. Synthetic THC is FDA approved as **dronabinol** (**Marinol, Syndros**)
2. Synthetic THC analogue as **nabilone** (**Cesamet**)





# - Structure	Insult	Pathological Effect↑	Source
1 – Kidney	Primary/Secondary Hypertension	↑ AEA ↑ 2AG	72
1 – Kidney	Bilateral ischemia reperfusion model of AKI	↑ 2AG	73
1 – Kidney	Cisplatin – induced AKI	↑ AEA	35
2 – Renal cortex	UUO Model of Renal Fibrosis	↑ CB ₁ Expression ↑ 2AG	20
3 – Podocytes and mesangial cells	Diabetic Nephropathy	↑ CB ₁ Expression	19, 30
3 – Mesangial cells	Increased Glucose	↑ CB ₁ Expression	30
4 – Proximal tubule cells	Increased Albumin	↑ CB ₁ Expression	15
5 – Podocytes	STZ-induced Diabetic Nephropathy	↓ CB ₂ Expression	48
6 – Proximal tubule cells	Increased Glucose or Albumin	↓ CB ₂ Expression	34

Effect on kidney disease

- I. Symptoms associated with CKD and ESRD
- II. Impaired kidney function
- III. Acute kidney injury
- IV. Kidney transplantation



I. Symptoms associated with CKD and ESRD

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Causes of Chronic or Recurrent Pain in CKD

Comorbid illnesses

- Diabetic peripheral neuropathy
- Peripheral vascular disease

Cause of kidney failure

- Polycystic kidney disease

Syndromes unique to CKD

- Renal bone disease
- Dialysis-related amyloidosis
- Uremic peripheral neuropathy
- Calcific uremic arteriolopathy (calciphylaxis)
- Nephrogenic systemic fibrosis

Syndromes common in or exacerbated by CKD

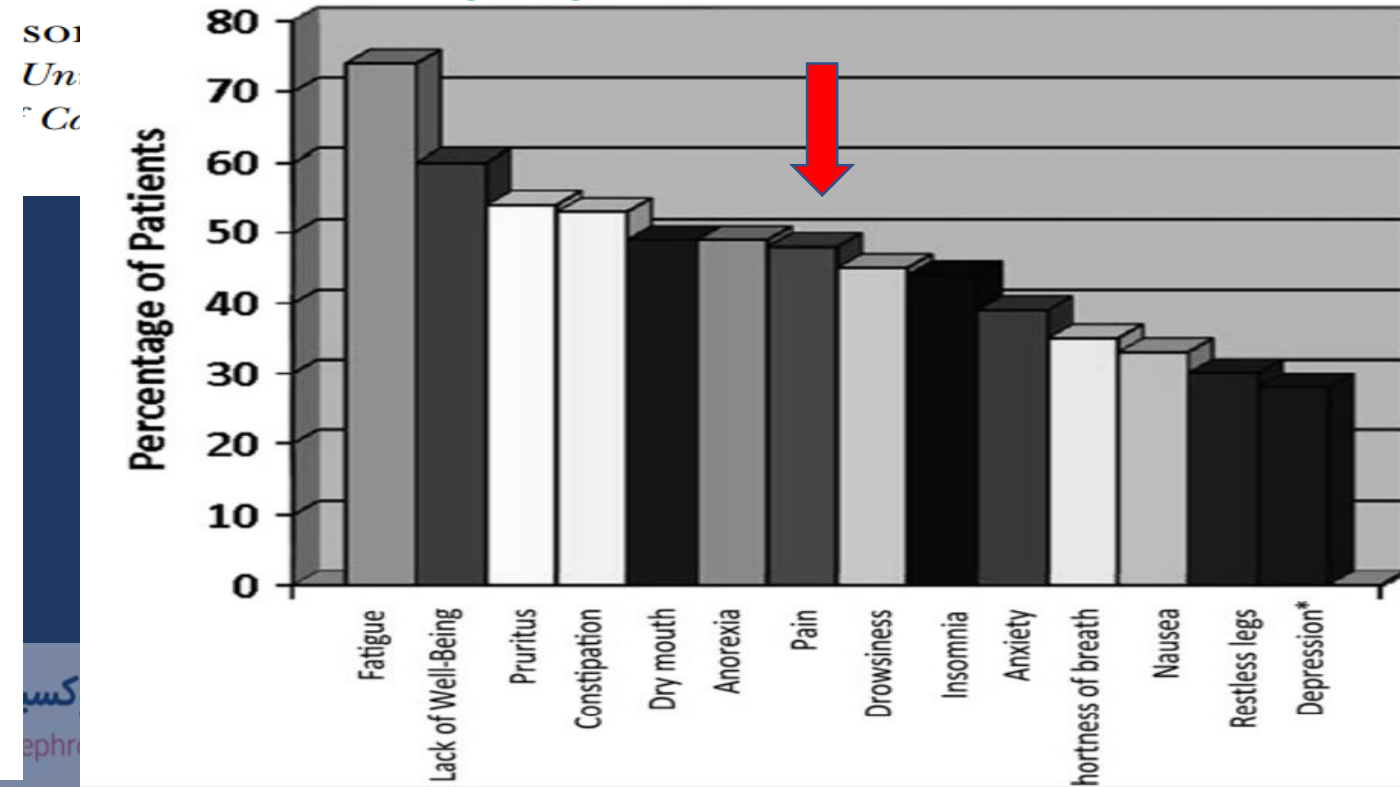
- Inflammatory arthritis
- Osteoarthritis
- Osteoporosis

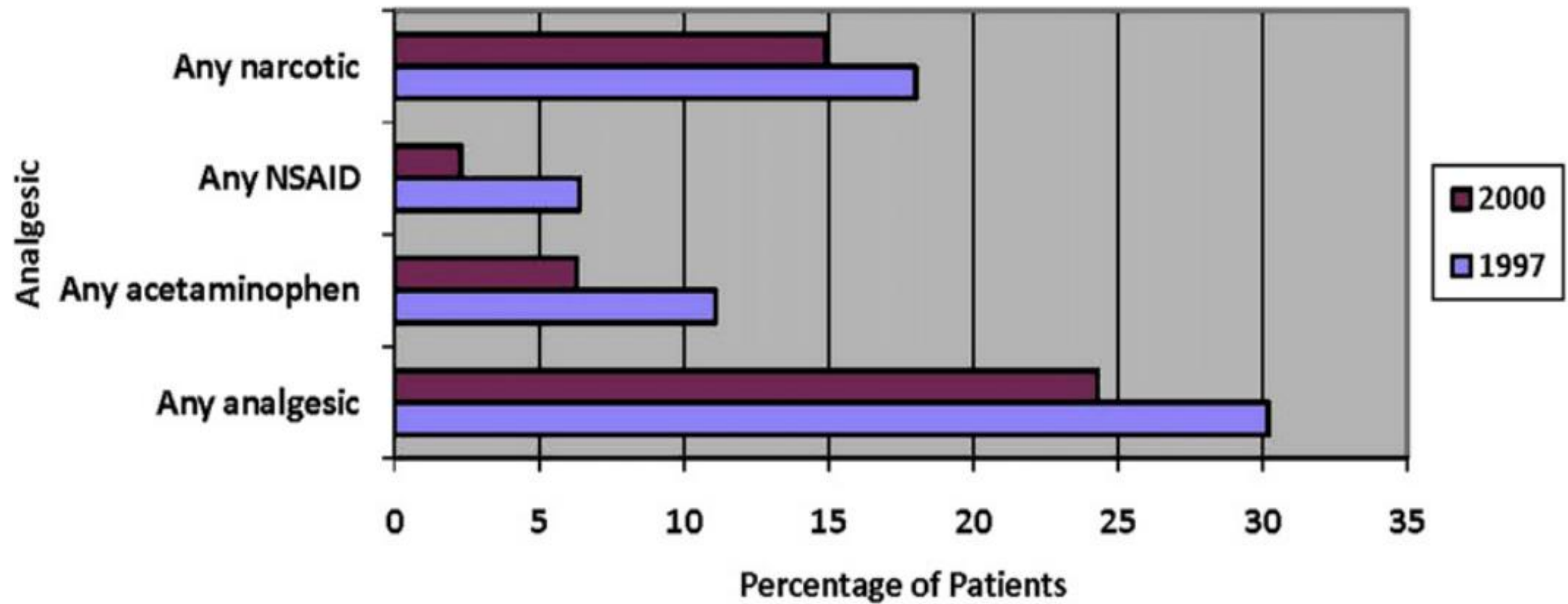
Complications of the dialysis procedure

- Recurrent pain while on dialysis: cramps, headaches, and needling of arteriovenous fistula
- Discitis/osteomyelitis from central venous catheters (dialysis access)
- Vascular steal from arteriovenous fistulae (dialysis access)
- Lower back strain from abdominal distension with peritoneal dialysis

Role of Cannabinoids in Chronic Kidney

Symptom burden in CKD





- ✓ 25-50% CKD patients experiencing chronic symptoms such as pain, nausea, anorexia, sleep disturbance, anxiety, and depression
- ✓ Over 60% of dialysis patients receive at least one opioid, annually
- ✓ Approximately 20% of them take prescription opioids, chronically.



Table 1. Potential Benefits of Medical Marijuana Use for Symptoms of Advanced CKD and ESRD

	Rationale for Use	Comments
Chronic pain	Evidence for treating chronic pain ²⁸	Legalization of medical marijuana has been associated with <u>decreases in opioid-related hospitalizations³⁴ and overdose deaths³⁵</u>
Nausea	Substantial evidence for treating chemotherapy-induced nausea and vomiting ²⁸ ; FDA-approved to treat chemotherapy-induced nausea and vomiting	Evidence <u>limited to chemotherapy-induced nausea and vomiting</u>
Anorexia and cachexia	Anecdotal evidence of appetite stimulation; FDA-approved to treat anorexia associated with AIDS	<u>Limited evidence base mostly focused on AIDS population</u>
Pruritus	Preclinical evidence suggests a role of CB1 in the central nervous system response to itch ⁴² ; emollient containing endocannabinoids effectively treated uremic pruritus in a small trial ⁴³	<u>Lack of effective treatments; could be studied as a secondary outcome in studies focused on other indications</u>

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; FDA, US Food and Drug Administration.



Indication	Comments
Anorexia/cachexia	AIDS patients have experienced a substantial improvement in appetite with dronabinol that was sustained for more than 12 months and associated with a modest (2 kg) increase in lean body mass. ⁴⁵
Pruritus	Topical CBs were effective in 21 hemodialysis patients with uremic pruritus. ⁴⁶ Dronabinol was effective in three patients with intractable pruritus secondary to cholestatic liver disease. ⁴⁷
Insomnia	It remains unclear how, if at all, CBs alter sleep patterns. THC has been found to be sedative, whereas CBD appears to have alerting properties. Numerous clinical studies report significantly improved sleep quality in patients taking CBs for symptomatic treatment of multiple sclerosis, chronic pain, or intractable pruritus. Beneficial effects may be, in large part, a result of improved symptom control.
Anxiety/depression	CB _{2R} agonists are thought to have anxiolytic and antidepressant properties but good data are currently lacking.
Cardiovascular stability	CB _{1R} and especially CB _{2R} agonists limit cardiac infarct size induced by ischemia-reperfusion injury, and CB _{2R} agonists inhibit the progression of established atherosclerotic lesions in animal models. Pretreatment with CB _{1/2R} agonists improves endothelial cell dysfunction and survival in both cardiogenic and endotoxic shock. ^{25,26}

AIDS = acquired immunodeficiency syndrome.



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case-control study(716 ESRD pts started therapy in 1991 /361 control)

Recreational Drug Use: A Neglected Risk Factor for End-Stage Renal Disease

Thomas V. Perneger, MD, PhD, Michael J. Klag, MD, MPH, and Paul K. Whelton, MD, MSc

Table 4. Odds Ratios of ESRD for Lifetime Use of Various Drugs in Community-Based Case-Control Study of ESRD

	Unadjusted	Adjusted for All Other Drugs in Table	Adjusted for Age, Sex, Race, Socioeconomic Status,* Hypertension,† and Diabetes‡	Adjusted for Heroin and Other Opiate Use, Age, Sex, Race, Socioeconomic Status,* Hypertension,† and Diabetes‡
Heroin or other opiates	22.5 (3.1-163.9)	14.2 (1.8-111.6)	19.1 (1.7-208.7)	§
Cannabis	1.1 (0.8-1.4)	0.7 (0.5-1.0)	1.2 (0.7-2.1)	1.0 (0.5-1.8)
Amphetamines	1.5 (0.8-1.6)	1.1 (0.5-2.1)	1.7 (0.6-4.6)	1.1 (0.4-3.2)
Tranquilizers	0.8 (0.5-1.1)	0.6 (0.4-0.9)	0.9 (0.4-1.7)	0.7 (0.3-1.4)
Cocaine or crack	3.6 (1.9-6.8)	2.9 (1.3-6.5)	3.2 (1.2-8.6)	1.7 (0.5-5.5)
Psychedelics	3.4 (1.2-9.7)	1.5 (0.4-6.3)	5.0 (1.0-26.0)	2.6 (0.5-15.1)

NOTE. Values expressed as odds ratio (95% CI) for ever versus never used drug.

*Measured by three variables: education level (0 to 6, 7 to 11, 12, 13 to 16, or 17 to 24 years of education), insurance status (private or Medicare, health maintenance organization, Medicaid, or none), and dental status (missing teeth: none, 1 to 16, 17 to 31, or all).

†Duration of hypertension (<5, 5 to 14.9, or ≥15 years), hospitalization for hypertension.

‡Type of diabetes and duration (none, <15 years, or ≥15 years).

§Varies by model (see text); odds ratio between 12.0 and 24.7.

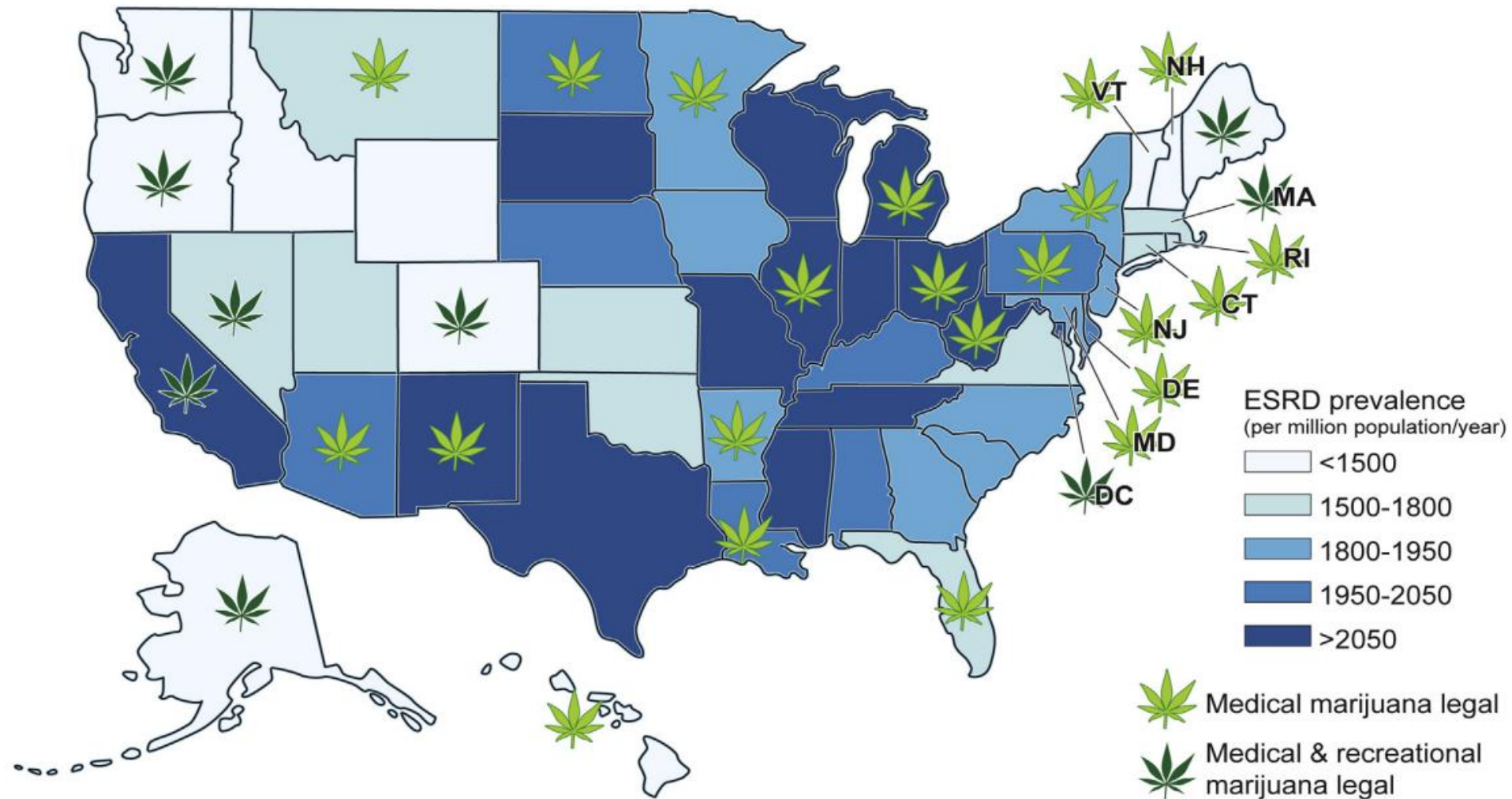


Figure 1. Map of the United States shows states with legalized use of medical or recreational marijuana, superimposed on the prevalence of end-stage renal disease (ESRD) by state. Reproduced with permission from Mount Sinai Health System.

Activate Windows

(CRIC) Study Chronic Renal Insufficiency Cohort

2003 to 2008 among 3939 adults

baseline eGFR between 20 and 70 ml/min/1.73 m²

No association between cannabis use and CKD progression over 5.5 years of follow-up



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(CARDIA) Study

Coronary Artery Risk Development in Young Adults

- ✓ 15 years of follow-up began 1988, in 3765 participants, Young Adults healthy individuals, (Past or current cannabis use was reported by 83% of participants).
- ✓ No association between cannabis use and eGFR change, rapid eGFR decline, or prevalent albuminuria



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(NHANES)

National Health and Nutrition Examination Survey

✓ cross-sectional analysis of 13 995, adults aged 18–59 years, from 2007 to 2014, self-reported past or current cannabis use.

✓ No clinically significant effect on serum creatinine, eGFR, microalbuminuria, or stage 2 or higher CKD



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(ASSESS-AKI) study

Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury

Multicenter, in USA, self-reported chronic cannabis usage (13%)

1,599 adults, 2009 to 2015, median F/U of 4.1 years

Baseline eGFR > 60 cc/m → marijuana use was not linked to incident CKD, or differences in eGFR slope over time

Baseline eGFR < 60 cc/m → eGFR declined more rapidly



- I. Symptoms associated with chronic kidney disease and end-stage renal disease
- II. Impaired kidney function
- III. Acute kidney injury
- IV. Kidney transplantation



ACUTE KIDNEY INJURY

- ✓ In 2012 report of acute kidney injury (AKI) due to synthetic cannabinoids. (**XLR-11, SPICE or K2,**)
Biopsy → ATN, AIN
- ✓ XLR-11 has been identified as a nephrotoxic compound (effects on proximal tubule mitochondrial function).
- ✓ Nausea, vomiting, and flank pain are common in the majority of cases.



Cannabinoid hyperemesis syndrome (CHS)

- ✓ Rare complication of heavy and frequent cannabis use over many years.
- ✓ Characterized by intractable vomiting that is relieved with hot showers.
- ✓ Occasionally associated with prerenal AKI, treated with IV fluids and antiemetics.
- ✓ Hypophosphatemia was observed in a case series of 6 men with CHS



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KIDNEY TRANSPLANTATION

- ✓ CB2R is widely expressed on immune cells and cannabinoids have *immunomodulatory effects* in animal models.



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The cannabinoid receptor 1 is involved in renal fibrosis during chronic allograft dysfunction: Proof of concept

J Cell Mol Med 2019; 23:7279–7288
Dao M, Lecru L, Vandermeersch S, et al

- ✓ significant upregulation of glomerular and tubular CB1 expression in those with chronic allograft dysfunction compared to low levels in normal kidney allografts, suggesting a role for CB1 in allograft fibrosis



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Recreational marijuana use is not associated with worse outcomes after renal transplantation

Clinical transplantation 30: 1340-1346, 2016.

- ✓ observational cohort of 1,225 kidney transplant recipients, recreational marijuana use
- ✓ Not associated with increased risk of death or worsening renal allograft function at one year post-transplant



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Cannabis dependence or abuse in kidney transplantation: implications for posttransplant outcomes

Transplantation 2019; 103:2373–2382

- ✓ Approximately two-fold increased risk of death-censored graft failure, all-cause graft loss, and death in the subsequent 2 years
- ✓ Posttransplant psychosocial complications, alcohol abuse, other drug abuse, schizophrenia, and depression, noncompliance, cardiovascular, pulmonary complications, accidents, and fractures.



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Delayed candidate listing or ineligibility ?

Transplant recipients

- ✓ Adherence to immunosuppressive medications
- ✓ Ability to follow instructions,
- ✓ Attendance of follow-up appointments



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Kidney and Nephrotoxins

۱۳-۱۵ مهر ۱۴۰۱-تهران

Marijuana use should not preclude consideration for kidney transplantation

Clin Transplant 2019; 33:e13706
Fabbri KR, Anderson-Haag TL,.. et al

A single center study of 919 kidney transplant recipients from 2001 to 2015 revealed that smoking status was not significantly associated with acute rejection, eGFR, or pneumonia within 1-year posttransplant.

Patients with isolated cannabis use had similar overall graft survival compared to nonusers



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Should donors who have used marijuana be considered candidates for living kidney donation?

Clin Kidney J 2019; 12:437–442 Ruckle D, Keheila M, West B, et al.

- ✓ Retrospective, single center study ,294 living kidney donors F/U 2.1 years and 230 recipients F/U 5.2 years (2000 and 2016).
- ✓ No deleterious effects on donor or recipient posttransplantation eGFR over a mean follow up.
- ✓ ACUTE REJECTION, GRAFT & PATIENT SURVIVAL WERE SIMILAR.



Extreme' vs recreational users?

Based on existing evidence, cannabis usage alone should not be the sole deciding factor for declining a patient for kidney transplant listing.



MEDICATION INTERACTION

- ✓ CBD inhibits hepatic cyclosporine metabolism in vitro and in mice
- ✓ Several case reports demonstrate increased tacrolimus levels associated with CBD
- ✓ Inaccurate product labeling and batch to batch variability of CBD products may lead to unpredictable CNI levels, potential toxicity, or underdosing, especially with intermittent use of different cannabinoid products.



HOME MESSAGE

- I. Symptoms associated with CKD and ESRD → SOME EVIDENCE
- II. Impaired kidney function → NO PROOF
- III. Acute kidney injury → SPECIALL SITUATION
- IV. Kidney transplantation → INTERACTIONS, GRAFT SURVIVAL, ELIGIBILITY



THANKS FOR YOUR ATTENTION



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صائب تبریزی

در آن زلف سیه دل‌های خونین می شود پیدا

در آن سنبلستان آهوی مشکین می شود پیدا

به نومیدی مده از دست خود دامن شبها را

که از خاک سیه گل‌های رنگین می شود پیدا

گرانی‌های غفلت لازم افتادست دولت را

که در جوش بهاران خواب سنگین می شود پیدا

سبک روحانه سرکن گرسبکساری طمع داری

که در دل کوه غم از کوه تمکین می شود پیدا

ز حرف عشق، صائب میروند افسردگان از جا

اگر در مرده‌ها جنبش ز تلقین می شود پیدا

