INTERACCIONES FARMACOCINETICAS ENTRE CANNABIS Y OTROS MEDICAMENTOS

Prof. Marta Vázquez
Departamento de Ciencias Farmacéuticas
24 de junio 2020

UNIVERSIDAD DE LA REPUBLICA
URUGUAY

Química Farmacéutica, Doctor en Química
Facultad de Química, Universidad de la República, Montevideo, Uruguay.

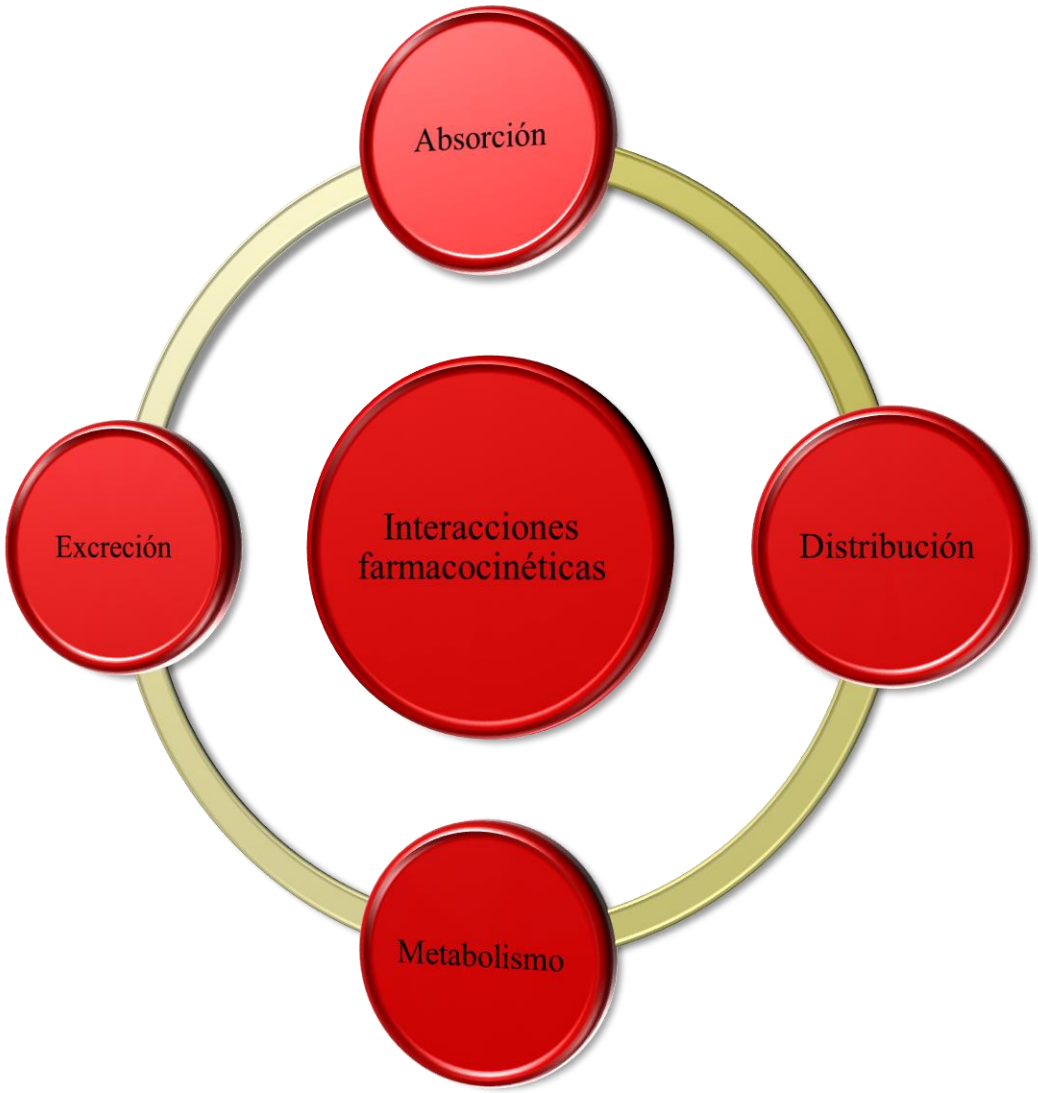
Posición Actual:
Profesora Titular del Departamento de Ciencias Farmacéuticas de la Facultad de Química (en régimen de Dedicación Total)
Dirección del Departamento de Ciencias Farmacéuticas
Dirección del Diploma de Especialista en Farmacia Hospitalaria
Encargada de la Unidad de Monitoreo de Medicamentos del Hospital de Clínicas (convenio Facultad de Química-Facultad de Medicina)
Dirección del Programa de Farmacia Clínica del Área de Biofarmacia y Terapéutica del Departamento
Dirección del Programa de Farmacovigilancia del Centro de Evaluación de Biodisponibilidad y Bioequivalencia de Medicamentos (Facultad de Química-Facultad de Medicina)
Dirección de Centro de Evaluación de Biodisponibilidad y Bioequivalencia de Medicamentos
Investigador del SNI (nivel II)

INTERACCIÓN FARMACOLÓGICA

Modificación del efecto de un fármaco causado por la administración conjunta de otros fármacos.

Interacciones farmacodinámicas

Interacciones farmacocinéticas


Absorción
Excreción
Interacciones farmacocinéticas
Distribución
Metabolismo

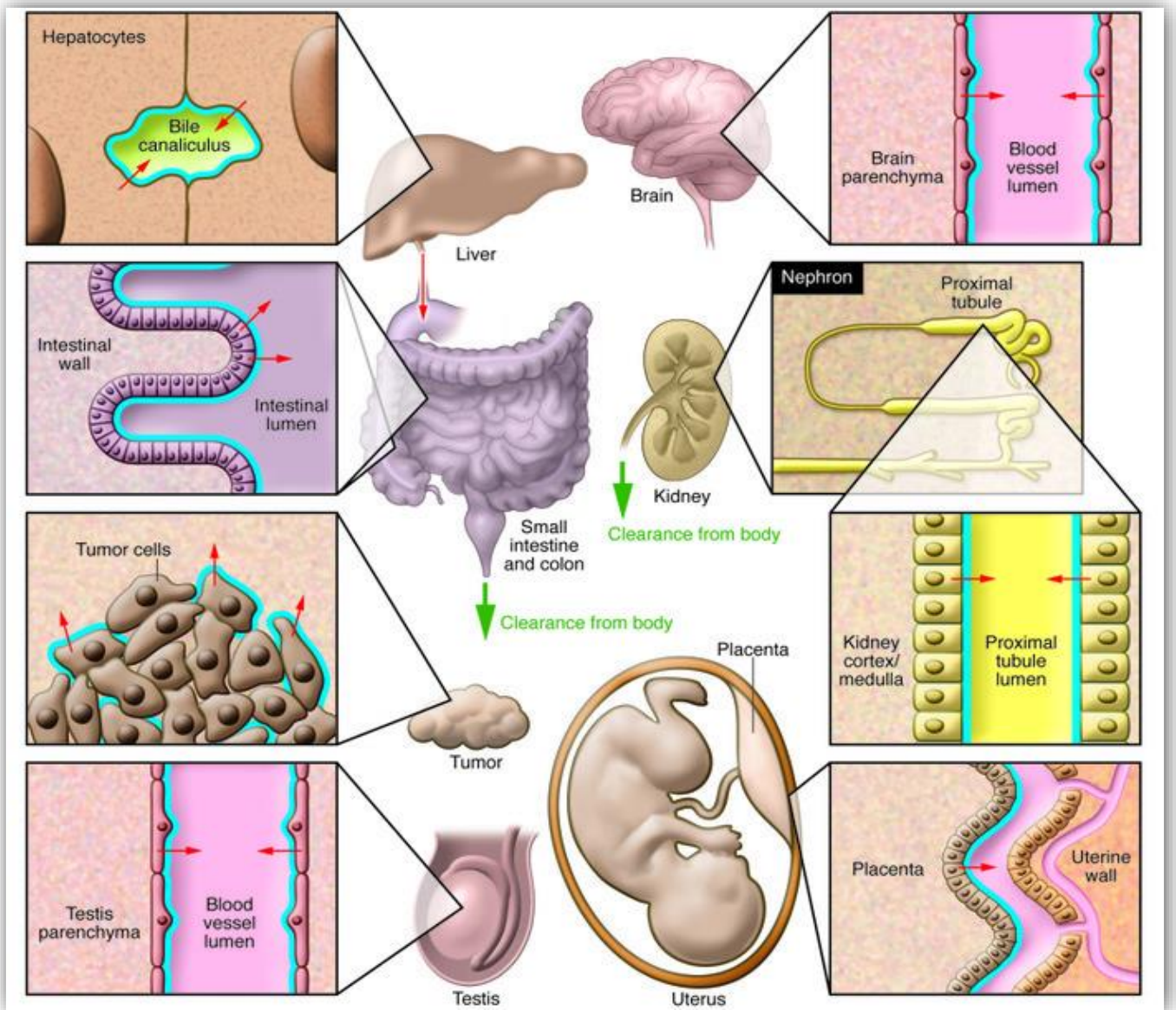
INHIBIDORES ENZIMATICOS

1A2	2C19	2C9	2D6	2E1	3A4,5,7
Cimetidina Quinilonas	Fluoxetina Ketoconazol Omeprazol	Amiodarona Fluconazol	Amiodarona Cimetidina Fluoxetina Haloperidol Ritonavir	Disulfiram	Indinavir Ritonavir Amiodarona Claritromicina Fluoxetina Ketoconazol Jugo pomelo

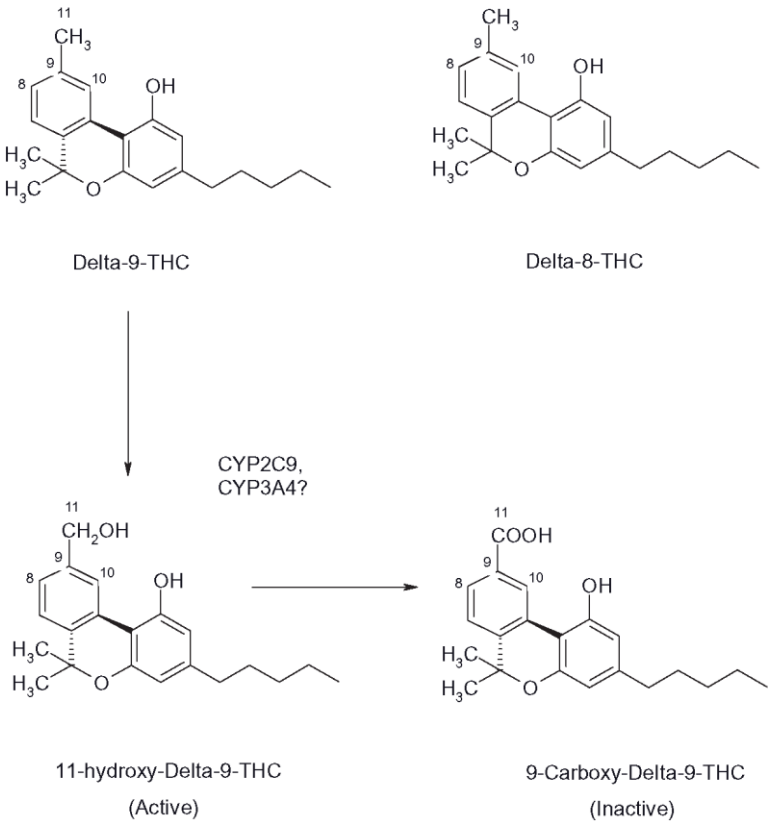
INDUCTORES ENZIMATICOS

1A2	2C19	2C9	2D6	2E1	3A4,5,7
Tabaco		Rifampicina		Etanol	Carbamacepina Fenobarbital Fenitoína

BOMBAS DE EFLUJO



METABOLISM O DE THC Y CBD



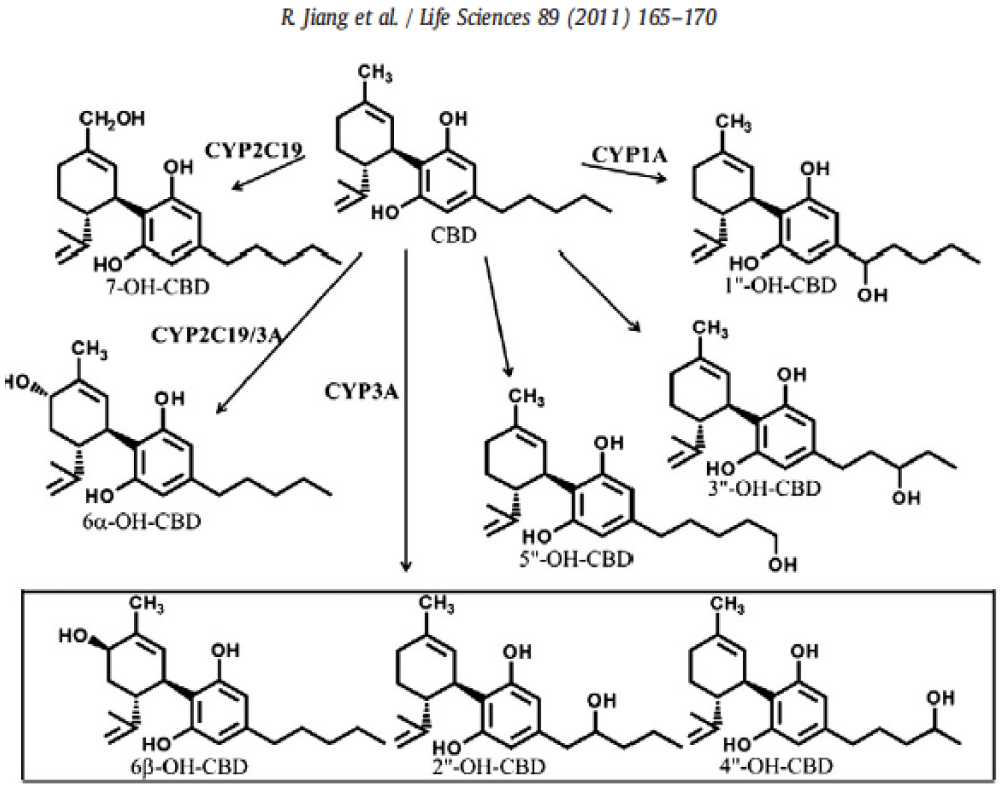


Fig. 5. Metabolic pathways of CBD in HLMs.

Cannabinoid Based Treatment and Interactions	Affected Transporters and/or Metabolic Enzymes	Experimental Results, Notes and Outcomes	References
Cannabis, THC, CBD, CBN with either chemotherapies, abuse drugs or medications	-Membrane transporters ABC super family (glycoprotein P; P-gp, Breast cancer-resistance protein; BCRP, and multidrug resistance protein; MRP1, 2, 3 and 4) -Cytochrome P450 (3A, 2D6, 2C9, 1A1, 1A2, 1B1, 2B6 and 2C8) -UDP-glucuronosyltransferases (UGTs)	-**P-gp, BCRP, and MRP1-4** transporters expression were dysregulated by cannabinoids, but in higher concentrations than that usually measured in cannabis smokers. -**CYP3A** was competitively inhibited by THC, CBD and CBN, with CBD being the most potent in a concentration compatible with that in usual cannabis inhalation. -**CYP2D6** was inhibited by THC, CBD and CBN, with CBD being the most potent in a higher concentration than that in usual cannabis consumption. -**CYP2C9** was inhibited by THC, CBD and CBN, with CBD inhibitory effect being dependent on the used substrates. -**CYP1A1**, **1A2**, **1B1**, **2B6**, **2C19**, **3A4** and **2C8** were strongly inhibited by CBD. -**UGT1A9**, and **2B7** were inhibited by CBD. -**UGT1A7**, **1A8**, and **1A9** were inhibited by CBN. -**UGT2B7** was activated by CBN. • Cannabinoids and drugs with inhibitory or stimulatory effects on UGT2B7 will interact. • Clinical studies are warranted to explore the potential interactions with chemotherapy, alcohol, abuse drugs, and prescription medications.	[17,50,51]
Δ^9-THC, CBD and marijuana inhalation with psychotropic agents	-Cytochrome P450	-**CYP2C9** and **CYP3A4** were inhibited by Δ^9-THC. -**CYP2C19** and **CYP3A4** were inhibited by CBD. -**CYP1A1** and **CYP1A2** were induced by marijuana inhalation. • Cannabinoids consumption via pyrolysis induced CYP due to aromatic hydrocarbons. • The effect of cannabinoids on the CYP activity influenced by the formulation, administration route, and derivation (Plant based or synthetic). • Clinical studies are warranted to explore the potential drug–drug interactions with cannabinoids.	[52]
Cannabinoids on other drugs	Cytochrome P450	-**CYP3A4** inhibitors and stimulators affect the elimination of Δ^9-THC and CBD. • Reviewed the pharmacokinetic interactions between cannabinoids on other drugs. • Limited data on the drug's effects on the accumulation of cannabinoids and marijuana. More clinical studies are warranted.	[53]
CBD with antiepileptic drugs	Cytochrome P450 or unknown	**Clinical studies of DDI**: -Non-significant increase of the clobazam plasma level administered with CBD (n = 13 children) due to potent inhibition of **CYP2C19**. -Significant change of plasma level of N-desmethylclobazam by CBD co-administration while no significant change in the level of valproate, stiripentol and levetiracetam (n = 24 open label trial). -All patients showed significant changes of the plasma levels of clobazam, N-desmethylclobazam, rufinamide, and topiramate by increasing CBD doses. The mean therapeutic range was exceeded for clobazam and N-desmethylclobazam; the plasma levels of eslicarbazepine and zonisamide were increased [median age = 3.6 years and 2 children]. • The purified CBD formula is FDA approved with antiepileptic drugs as a result of the published randomized clinical trials. • CBD is well tolerated with potential DDI and adverse effects. • The compulsory monitoring drug levels and patients' liver functions are advised.	[47,54]

Alsherbiny MA, Li CG. Medicinal Cannabis-Potential Drug Interactions. Medicines (Basel). 2018 ;6(1). pii: E3. doi: 10.3390/medicines6010003.

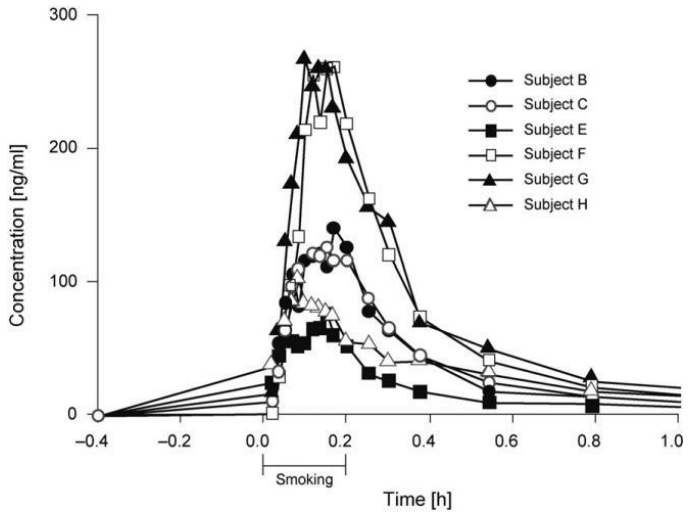
VÍAS DE ADMINISTRACIÓN

Puede administrarse prácticamente por cualquier vía (oral, intravenosa, rectal, transdérmica, inhalada, etc)

- Un modo de empleo muy común del cannabis es fumado: en cigarro o en pipa, mezclado o no con tabaco.

* Con el humo se inhalan, junto a los cannabinoides y otras moléculas de la planta del cannabis, hasta 2.000 sustancias diferentes producidas por la combustión.

- Biodisponibilidad por esta ruta: 2-56% (muy variable)

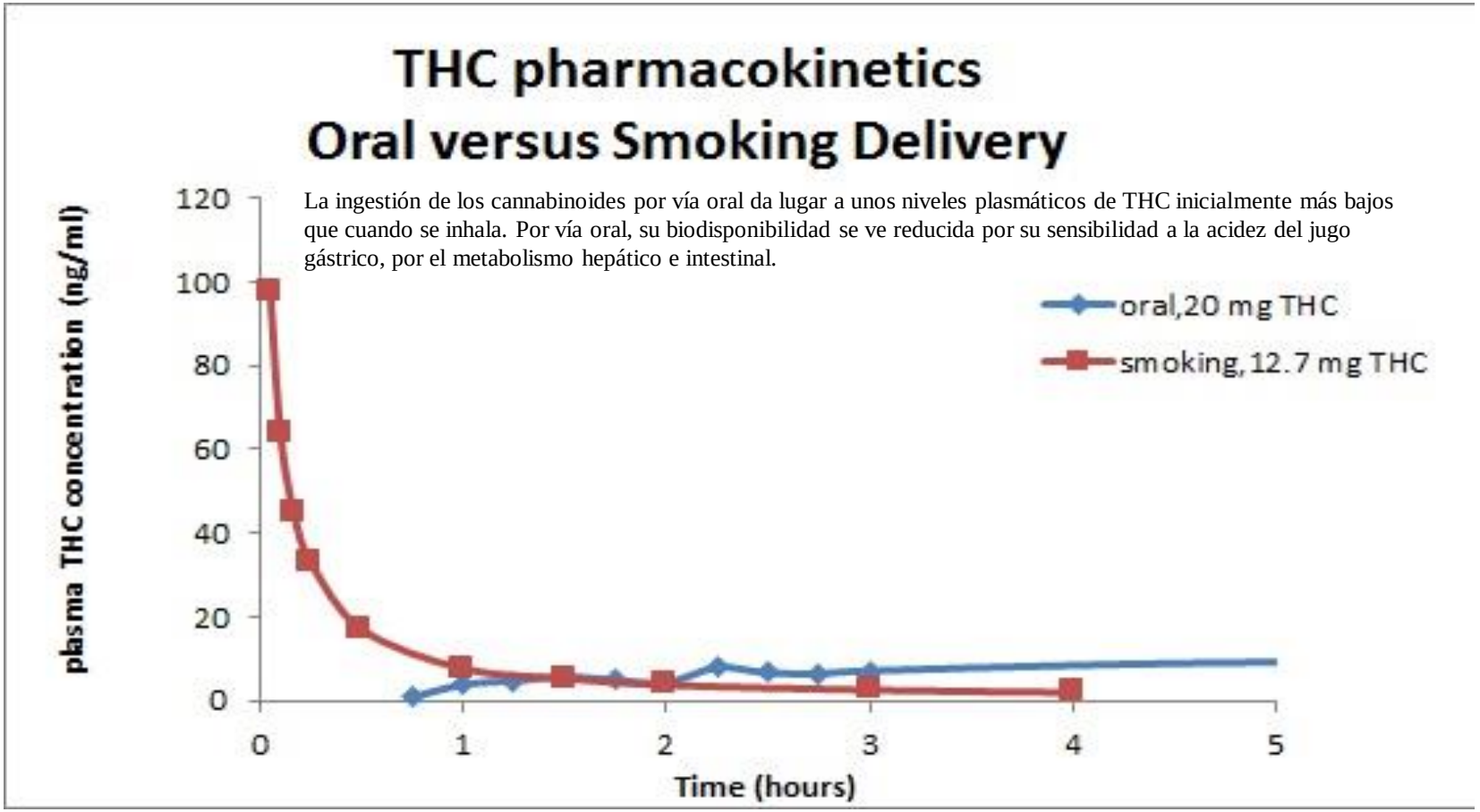


Time-dependent THC concentrations for six individuals (subjects B, C, and E–H) following smoking of a single cannabis cigarette containing **3.55% of THC.**

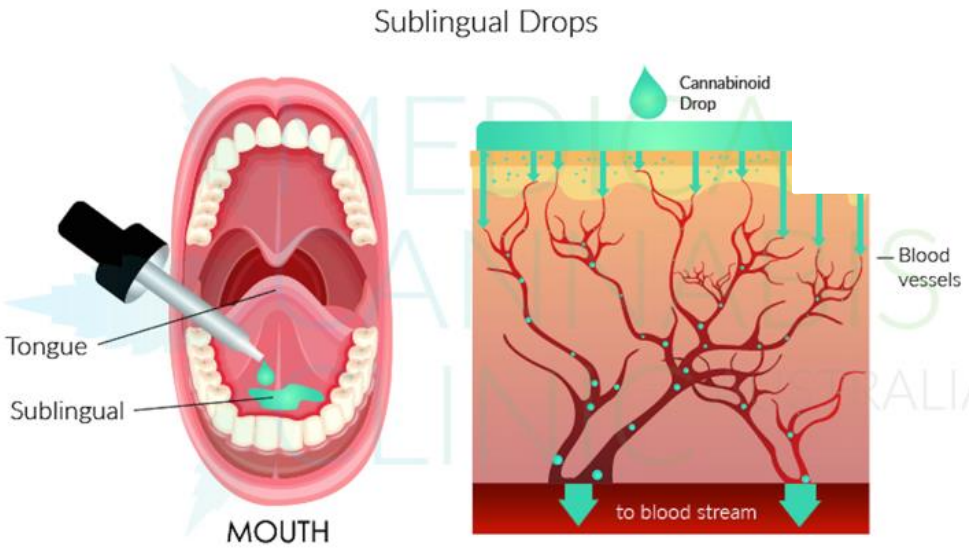
Huestis et al. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. J Anal Toxicol. 1992 Sep-Oct;16(5):276-82.

VÍAS DE ADMINISTRACIÓN

- Oral: en comparación con la via inhalatoria, el efecto se atrasa y las Cmax de THC y CBD son más bajas atribuible al efecto del primer paso de los cannabinoides pero la duración de los efectos es prolongada: 4-12 horas (biodisponibilidad 2-20%)



Vías de Administración

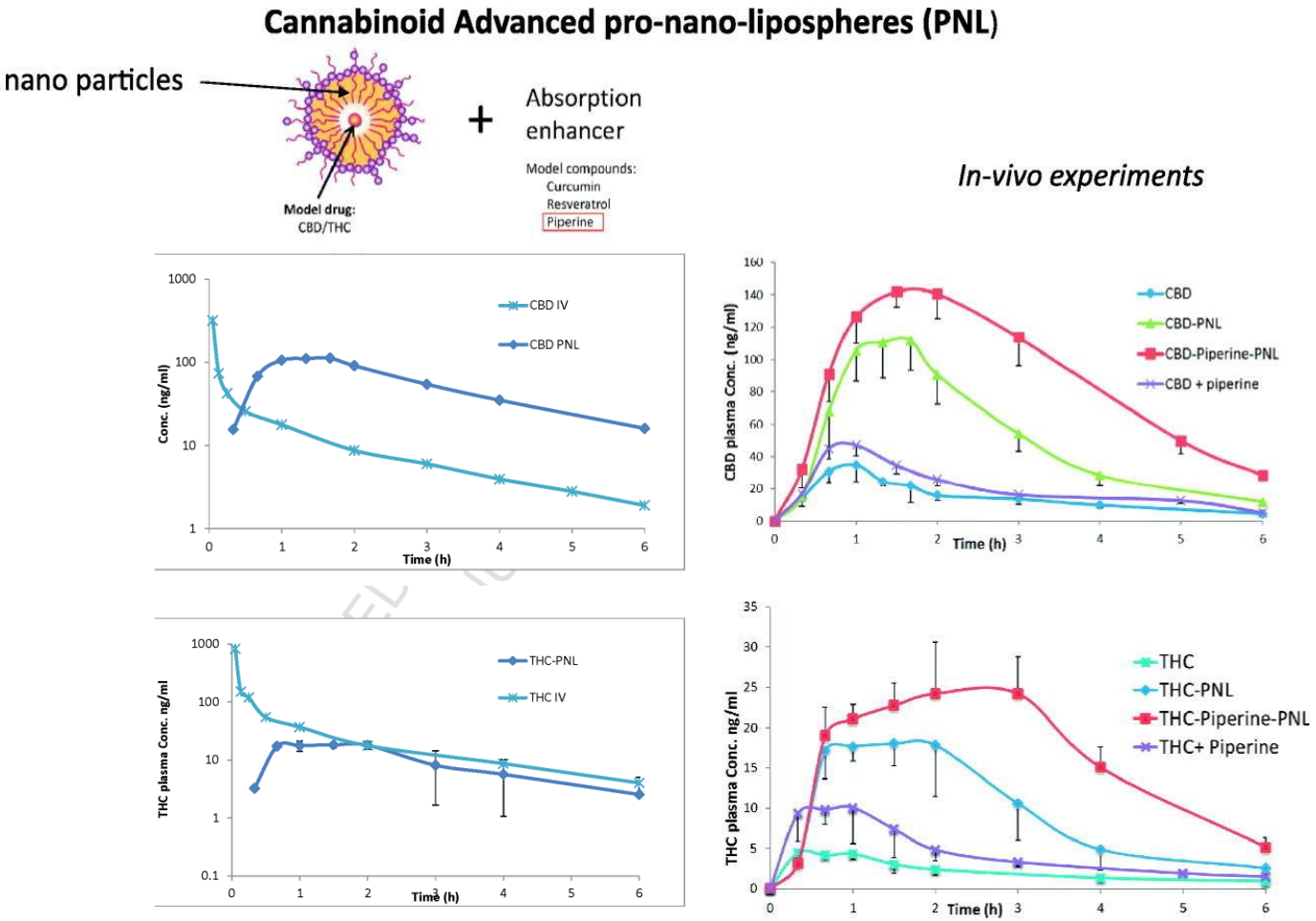


- Sublingual : transferencia directa a sangre evitando el metabolismo de primer paso

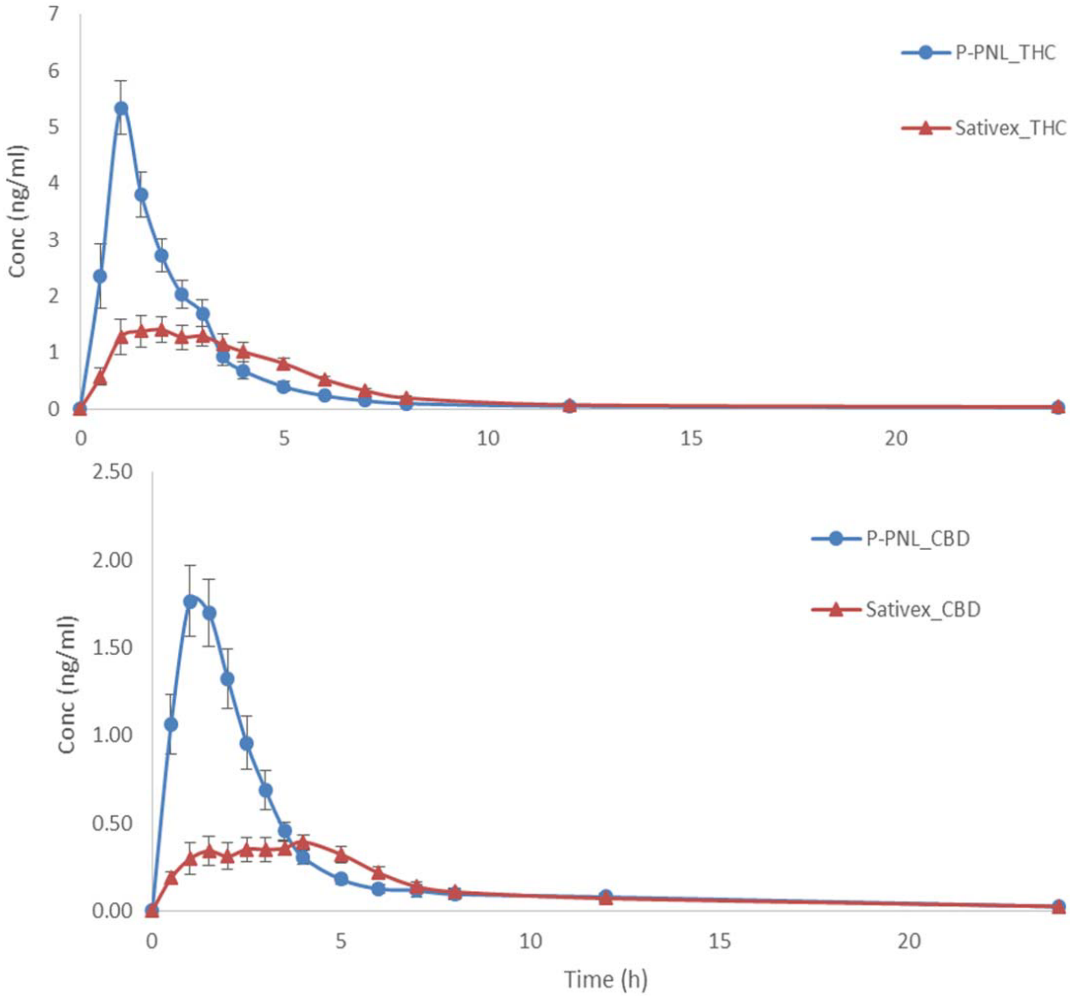
ABSORCIÓN

Cherniakov et al. The effect of Pro NanoLipospheres (PNL) formulation containing natural absorption enhancers on the oral bioavailability of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a rat model. European Journal of Pharmaceutical Sciences. 2017 Nov 15;109:21-30. doi: 10.1016/j.ejps.2017.07.003

Bhardwaj RK et al. Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4. J Pharmacol Exp Ther. 2002 Aug;302(2):645-50

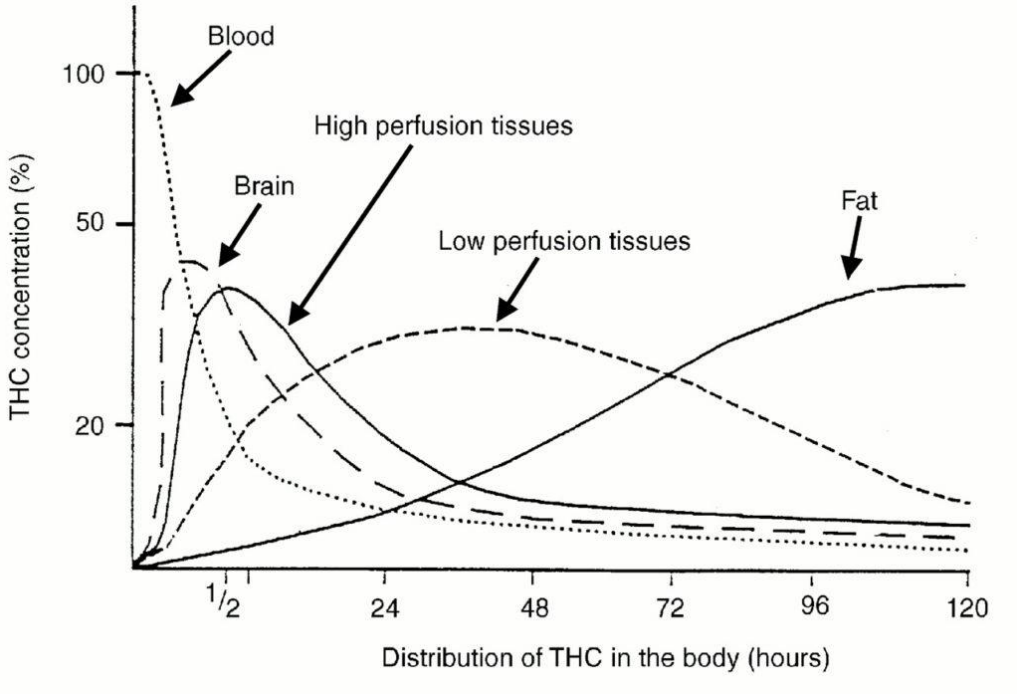


En voluntarios sanos



Cherniakov I et al. (2017). Piperine-pro-nanolipospheres as a novel oral delivery system of cannabinoids: Pharmacokinetic evaluation in healthy volunteers in comparison to buccal spray administration. Journal of Controlled Release 266: 1–7

Disposición



Disposición

- La paulatina liberación del THC, desde estos almacenes tisulares a la sangre, enlentece la caída de los niveles plasmáticos de este compuesto, tras el cese de su administración. Esto prolonga su presencia en sangre y la posterior entrada al cerebro. Esta podría ser la explicación de la ausencia de un síndrome de abstinencia, tras la suspensión de su ingesta, a diferencia de lo que ocurre en la adicción a opiáceos.

- En un fumador crónico la semivida de eliminación del THC está entre 3 y 5 días

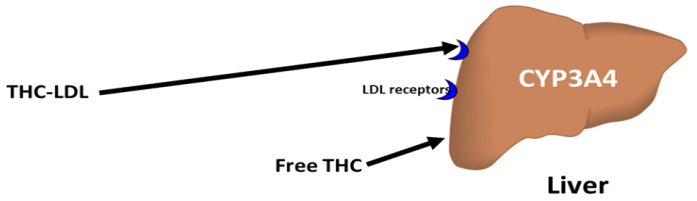
- La semivida de eliminación de CBD es de 1-2 días

Disposición

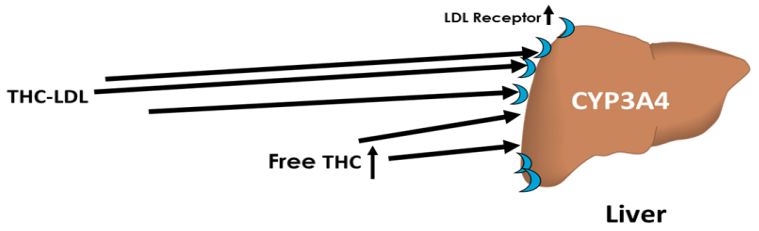
Solo un 3% del THC presente en sangre esta en forma libre.

Se une a diferentes componentes plasmáticos. Un 9% esta unido a las células sanguíneas. Otro 60% lo esta a las **LIPOPROTEÍNAS PLASMÁTICAS** y el resto a albúmina.

El CBD se une de forma similar.



A-THC-Elimination



B- THC-Elimination with statins

Disposición

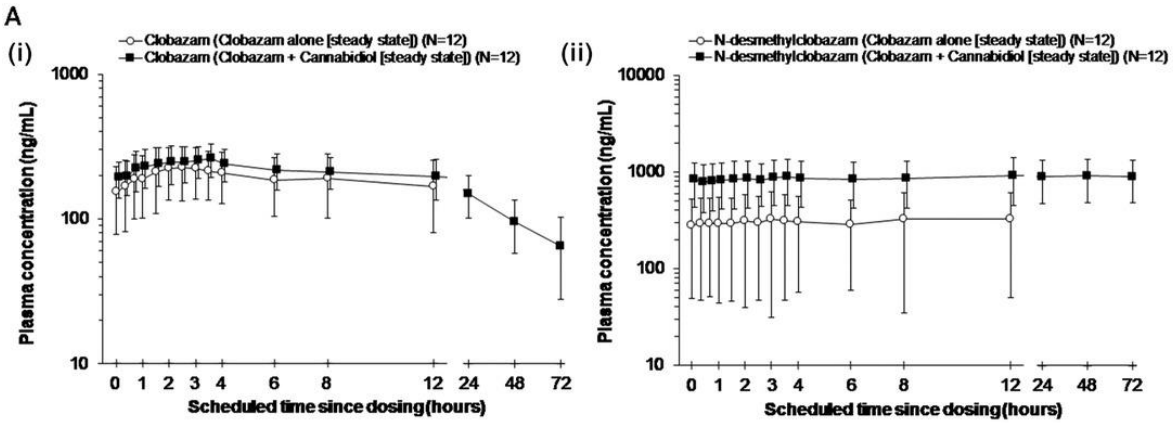
- Los cannabinoides atraviesan la placenta y se excretan por la leche materna durante la lactancia, llegando, como en el caso del THC, a concentraciones 8 veces superior que las plasmáticas. Por lo tanto, no se recomienda el uso de THC en el embarazo y la lactancia

- La eliminación del THC se produce principalmente mediante sus metabolitos en heces (un 68%) o en orina (12%), aunque también lo hace a través del pelo, la saliva y el sudor.

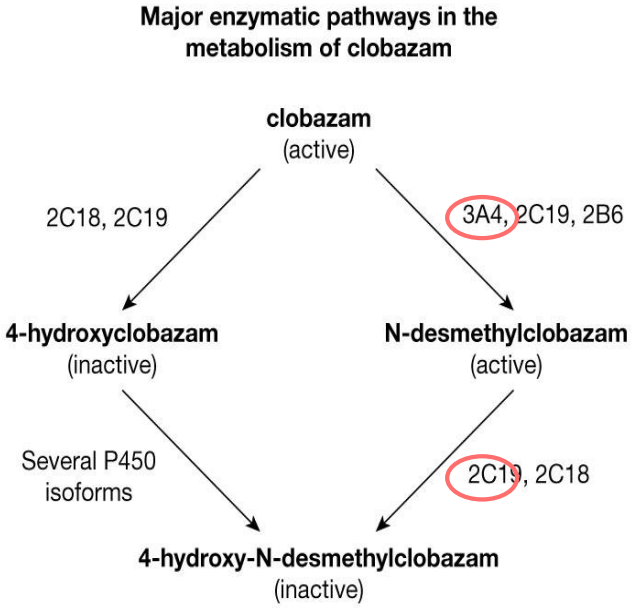
- La mayor parte del metabolismo ocurre en el hígado, aunque también puede producirse en el intestino.

CANNABIS Y EPILEPSIA

CBD y clobazam



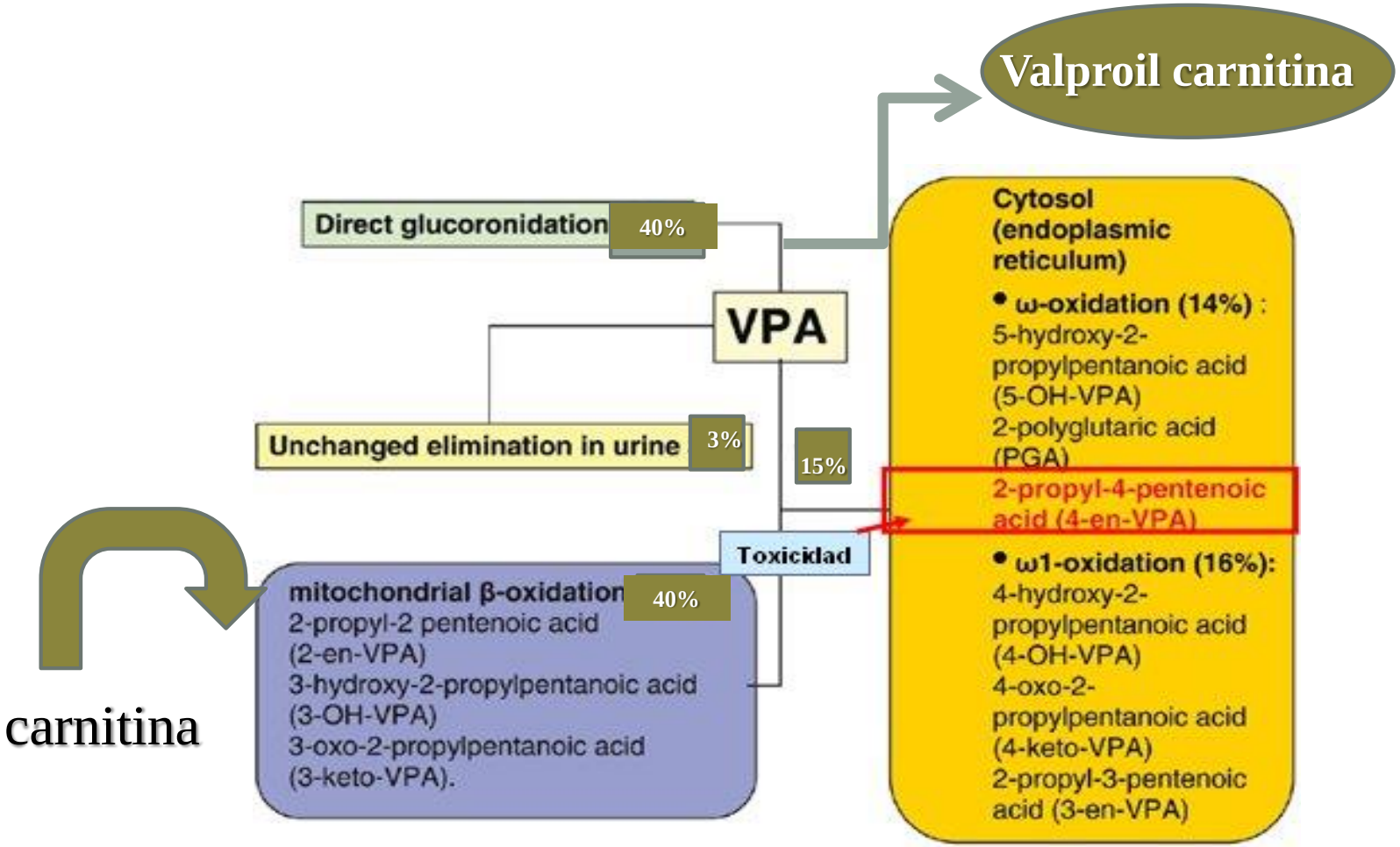
Mientras hay leves incrementos de los niveles de clobazam levels, el aumento observado para N-CLB es probablemente mediado por inhibición de CYP2C19.



-Morrison G et al. (2019). A Phase 1, Open-Label, Pharmacokinetic Trial to Investigate Possible Drug-Drug Interactions Between Clobazam, Stiripentol, or Valproate and Cannabidiol in Healthy Subjects. Clinical Pharmacology in Drug Development

-Geffrey A. L., Pollack, S. F., Bruno, P. L. and Thiele, E. A. (2015), Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia, 56: 1246–1251. doi:10.1111/epi.13060

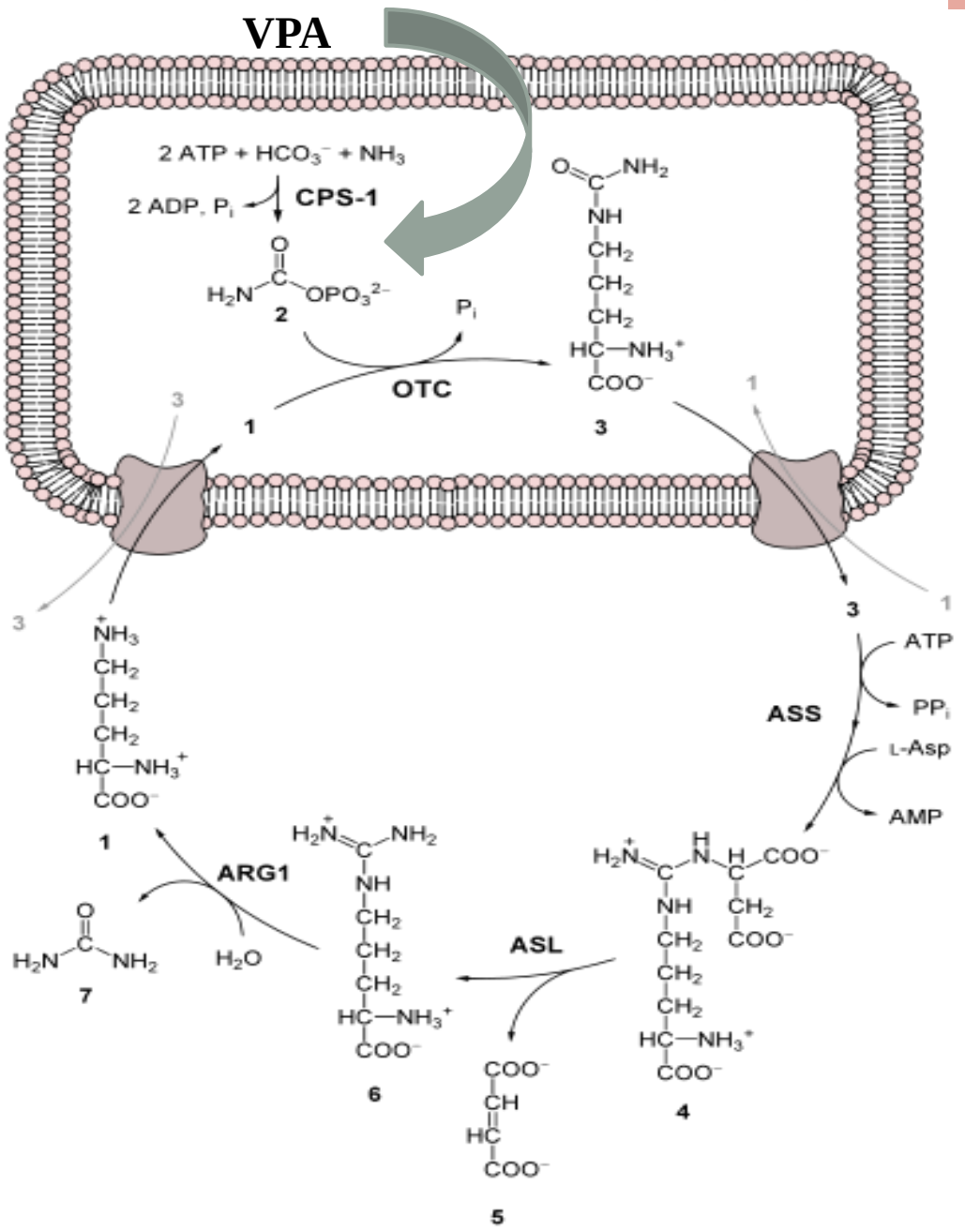
CBD y ácido valproico



CBD puede inhibir la glucuronidación de VPA y por lo tanto el clearance de VPA disminuiría resultando en concentraciones más altas de VPA → Más formación de metabolito hepatotóxico (4-en-VPA)

CICLO DE LA UREA

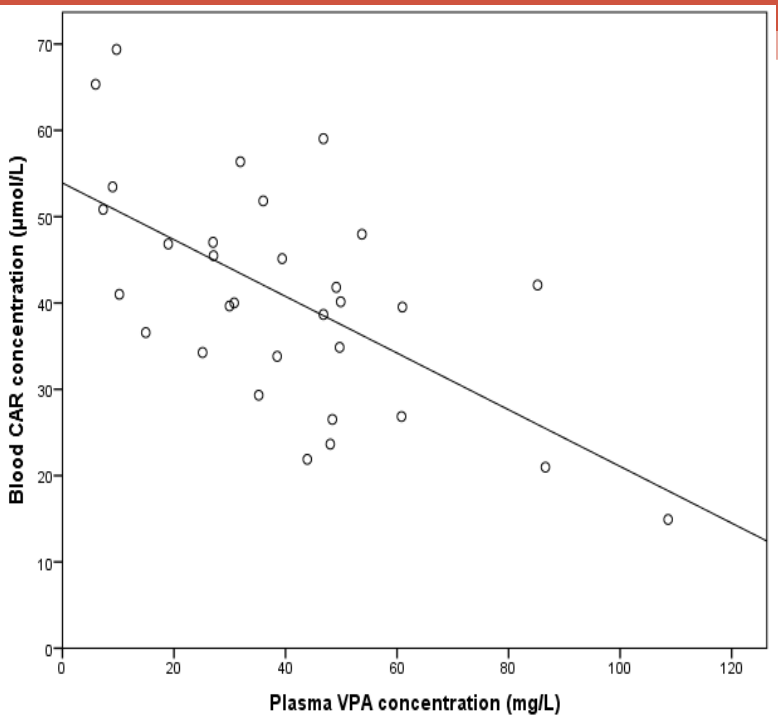
Inhibición por metabolitos del VPA



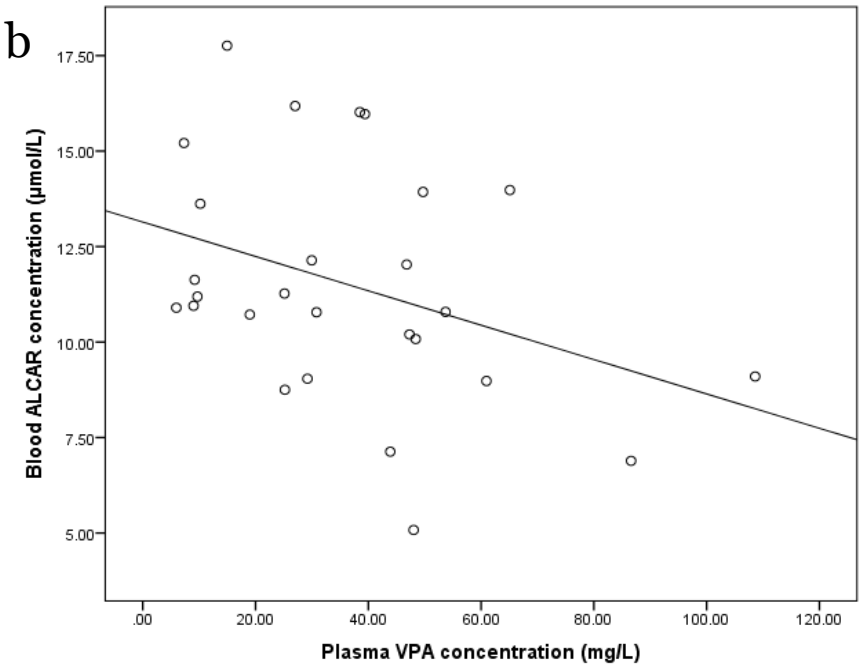
1 L-ornithine
2 carbamoyl phosphate
3 L-citrulline
4 argininosuccinate
5 fumarate
6 L-arginine
7 urea

L-Asp L-aspartate
CPS-1 carbamoyl phosphate synthetase I
OTC Ornithine transcarbamylase
ASS argininosuccinate synthetase
ASL argininosuccinate lyase
ARG1 Arginase|arginase 1

a



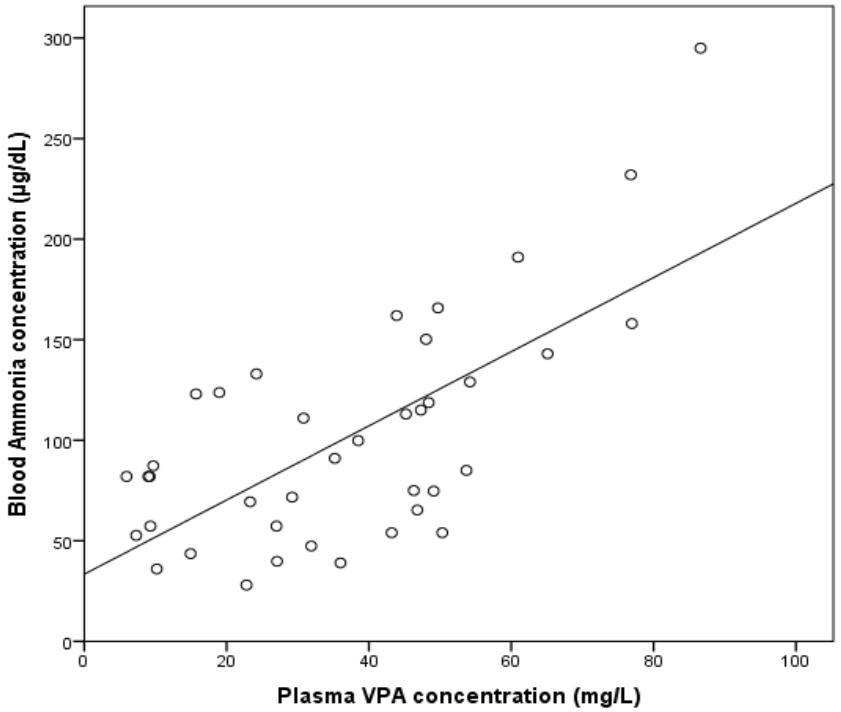
b



Relationship between plasma VPA concentration (a) Blood CAR concentration ($y = - 0.328x + 53.90$, $R^2 = 0.380$, $p < 0.0001$) and (b) Blood ALCAR concentration ($y = - 0.045x + 13.14$, $R^2 = 0.133$, $p = 0.062$).

Maldonado et al. Carnitine and/or acetylcarnitine deficiency as a cause of higher levels of ammonia. BioMed Research International, 2016

Relationship between plasma VPA concentration and Blood ammonia concentration (y=1.84x+33.41, R2=0.467, p<0.025);

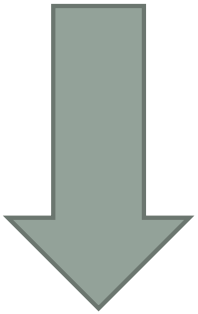


Maldonado et al. Carnitine and/or acetylcarnitine deficiency as a cause of higher levels of ammonia. BioMed Research International, 2016

Cannabidiol puede conjugarse por UGT1A7, UGT1A9, y UGT2B7

De acuerdo a estudios, el VPA puede inhibir UGT1A9 y UGT2B7.

Algunos autores no encontraron un cambio significativo de niveles de VPA con dosis crecientes de CBD pero sí un aumento de los niveles de AST y/o ALT después del tratamiento con CBD

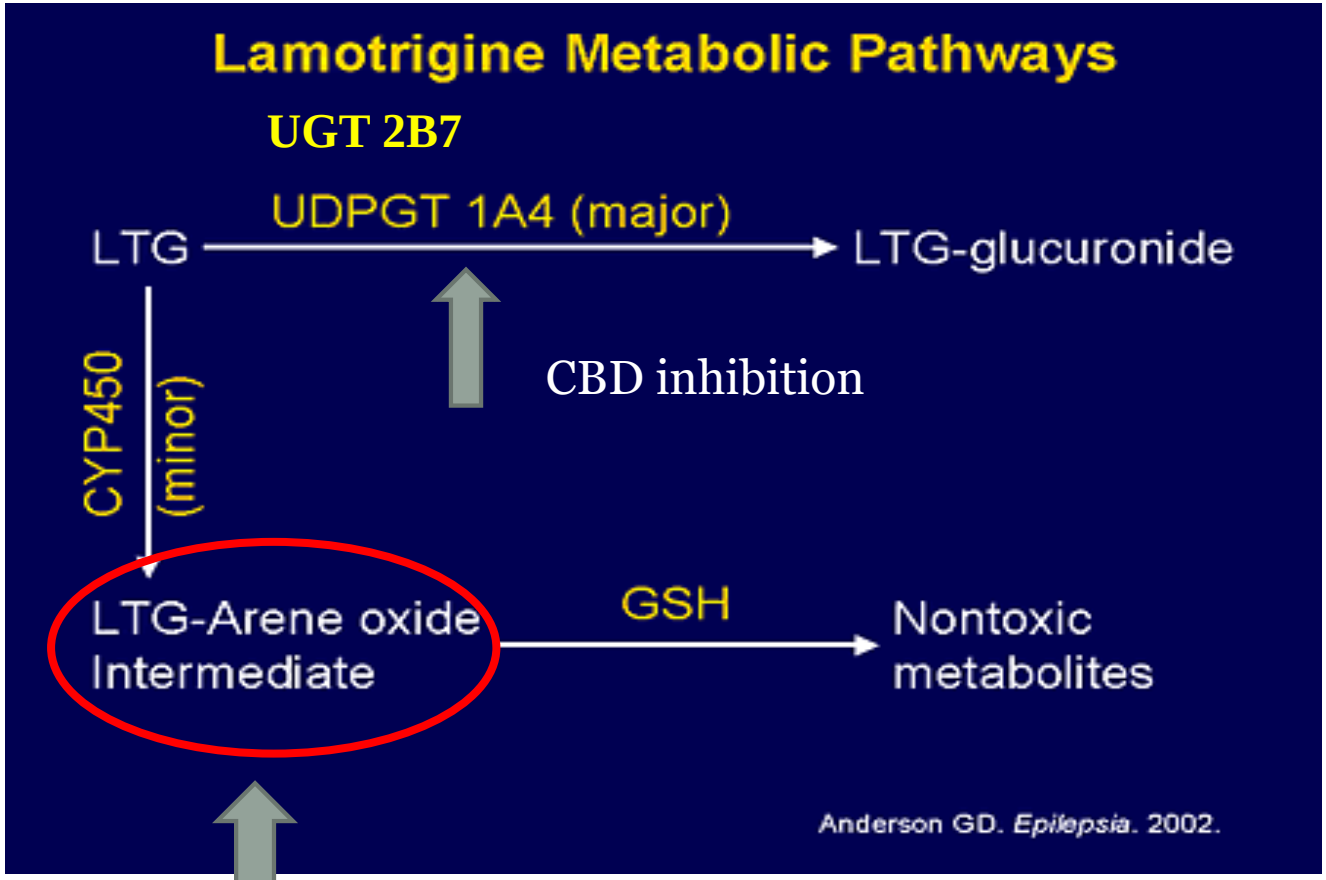


Niveles más altos de CBD  Hepatotoxicidad??

*Ewing, L.E.; et al . Hepatotoxicity of a Cannabidiol-Rich Cannabis Extract in the Mouse Model. Molecules **2019**, 24, 1694.*

Ethell BT, Anderson GD, Burchell B. The effect of valproic acid on drug and steroid glucuronidation by expressed human UDP-glucuronosyltransferases. Biochem Pharmacol. 2003; 65(9):1441-9.

CBD y lamotrigina



Un aumento de este intermediario puede resultar en daño celular y un aumento de riesgo de reacciones cutáneas.

Efectos de DAEs sobre los niveles de cannabinoides

El Fenobarbital, la Carbamacepina y la Fenitoína son inductores enzimáticos y por lo tanto se esperarían niveles más bajos de CBD

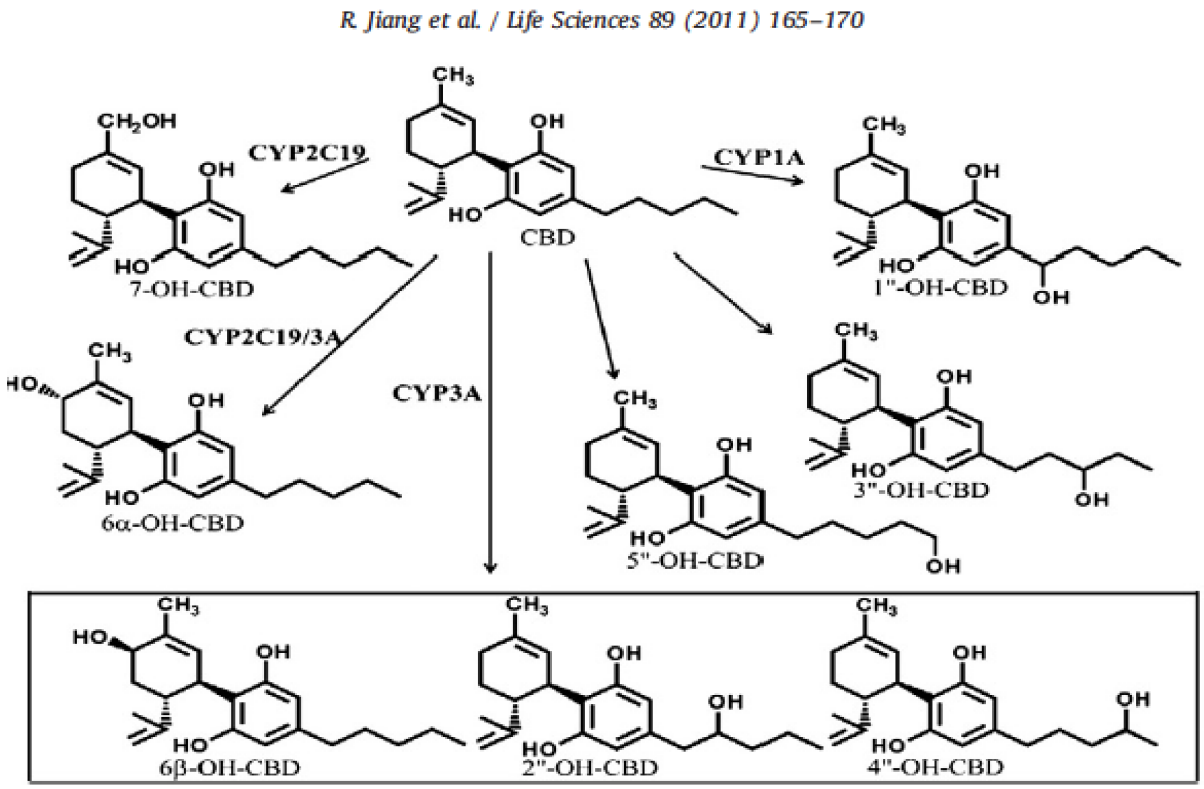
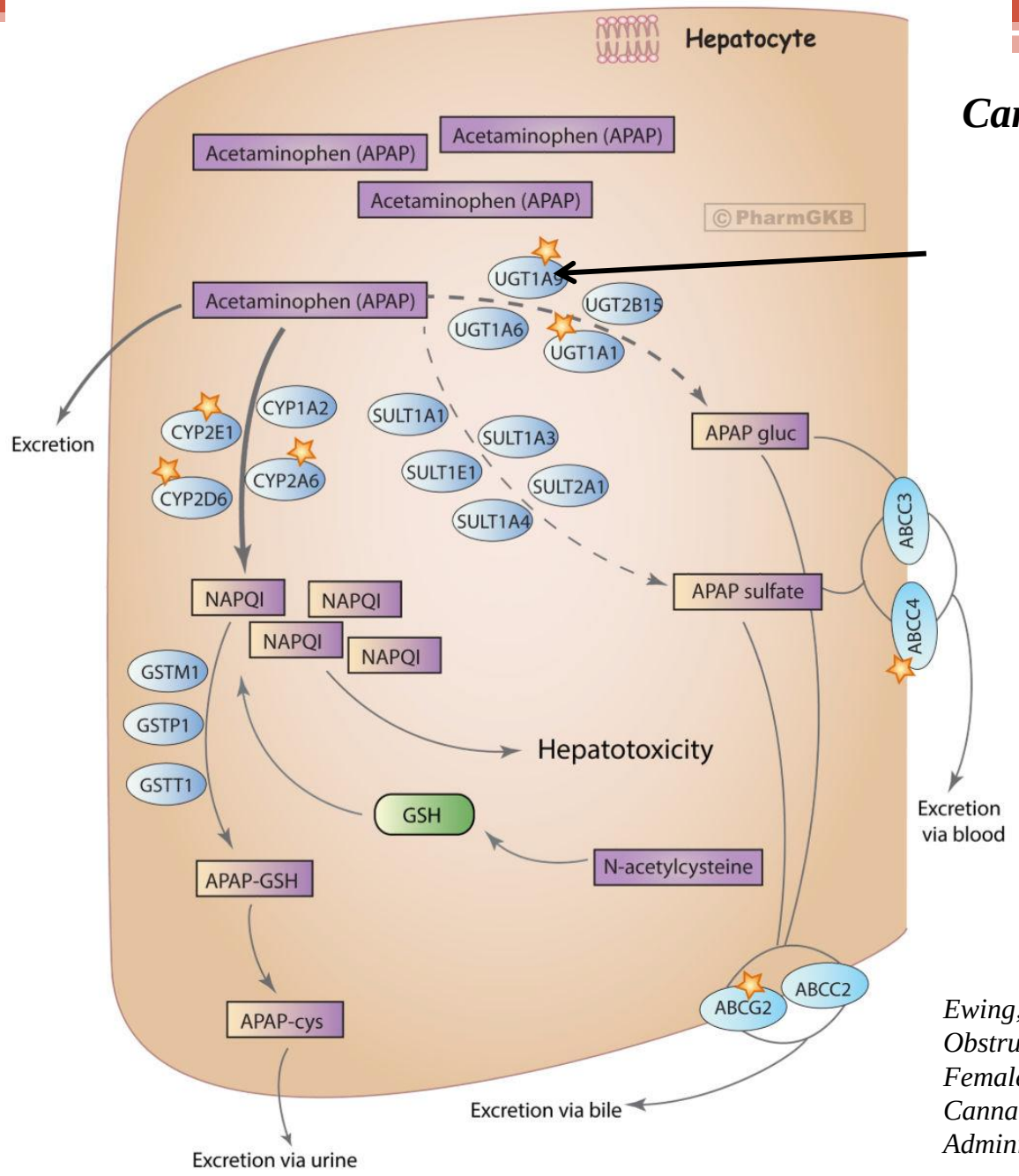


Fig. 5. Metabolic pathways of CBD in HLMs.

CANNABIS y ANALGESICOS

Cannabinoides-Acetaminofeno



Como el CBD puede inhibir UGTs, se esperaría una concentración más alta de paracetamol. Cuando la glucuronidación está comprometida, el paracetamol sigue otras rutas resultando a una sobreexposición del metabolito reactivo y hepatotóxico: NAPQI .

Ewing, L.E. et al. Paradoxical Patterns of Sinusoidal Obstruction Syndrome-Like Liver Injury in Aged Female CD-1 Mice Triggered by Cannabidiol-Rich Cannabis Extract and Acetaminophen Co-Administration. Molecules ***2019****, 24, 2256*

CBD y OPIODES

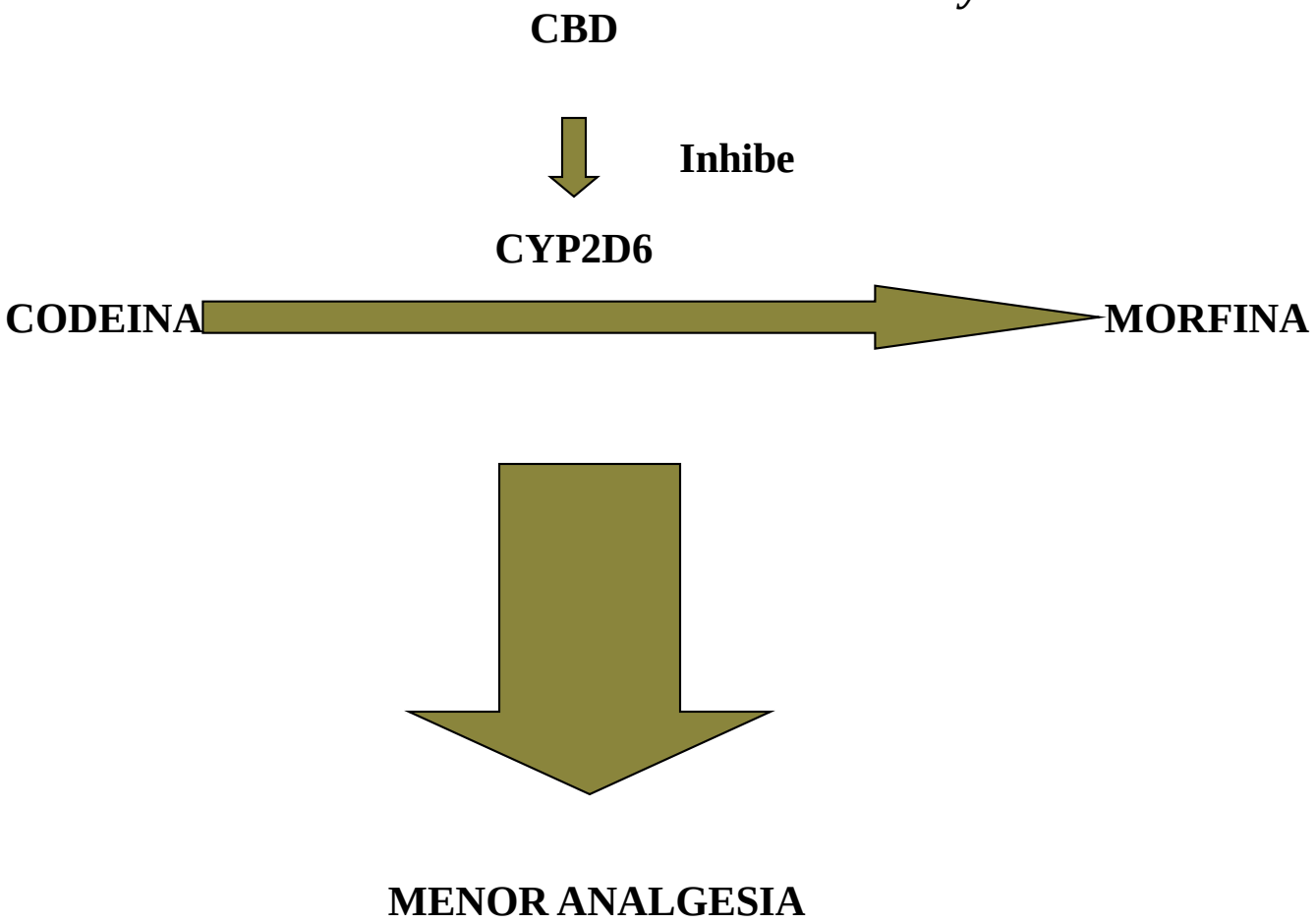
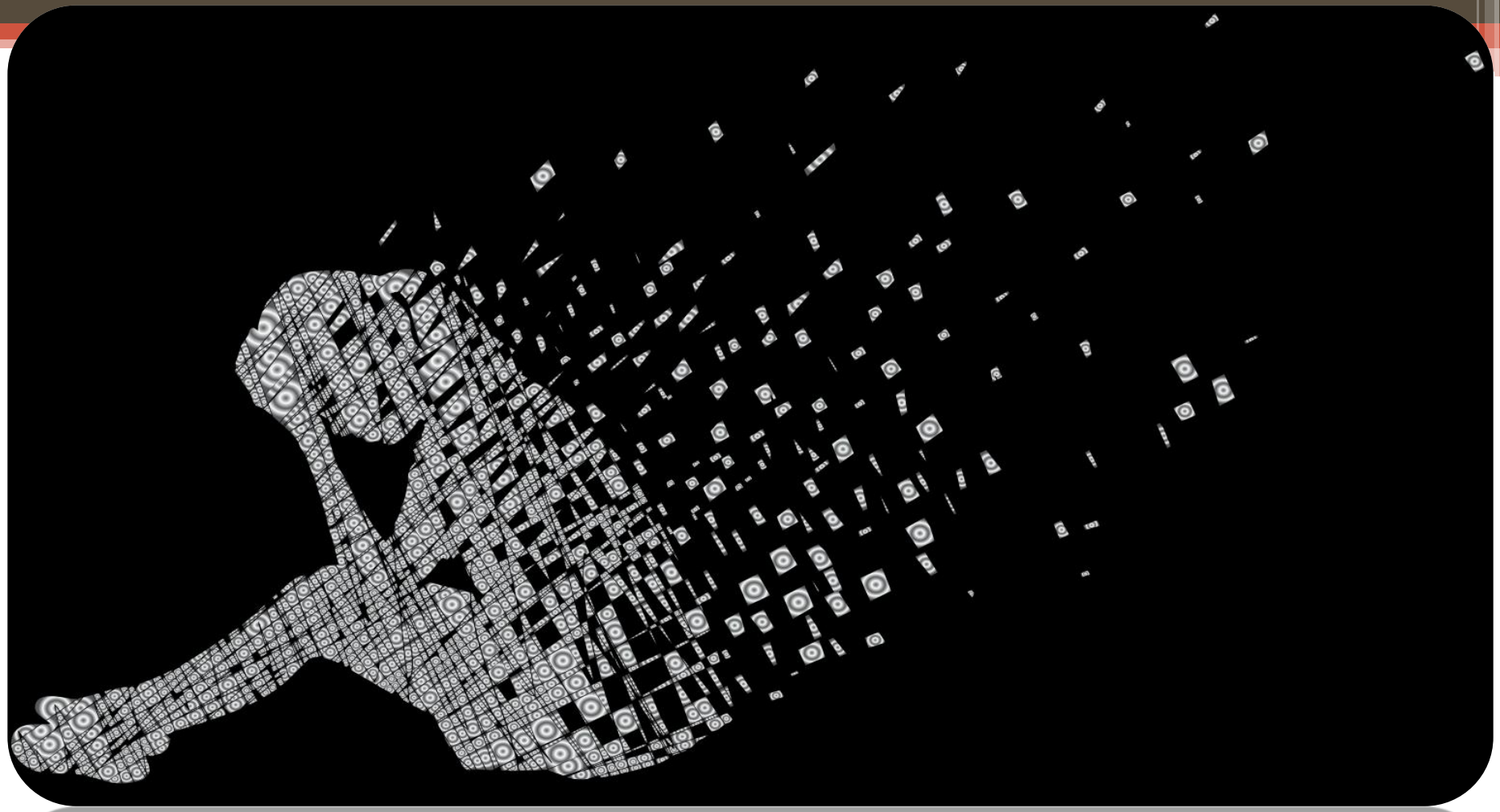


TABLE 1. **Metabolic Pathway/Enzyme Involvement**

Opioid	Phase 1 metabolism	Phase 2 metabolism	Comment
Morphine[12]	None	Glucuronidation via UGT2B7	
Codeine[13]	CYP2D6	None	
Hydrocodone[14]	CYP2D6	None	One of the metabolites of hydrocodone is hydromorphone, which undergoes phase 2 glucuronidation
Oxycodone[11]	CYP3A4 CYP2D6	None	Oxycodone produces a small amount of oxymorphone, which must undergo subsequent metabolism via glucuronidation
Methadone[15]	CYP3A4 CYP2B6 CYP2C8 CYP2C19 CYP2D6 CYP2C9	None	CYP3A4 and CYP2B6 are the primary enzymes involved in methadone metabolism; other enzymes play a relatively minor role
Tramadol[16]	CYP3A4 CYP2D6	None	
Fentanyl[10]	CYP3A4	None	
Hydromorphone[17]	None	Glucuronidation via UGT2B7	
Oxymorphone[18]	None	Glucuronidation via UGT2B7	

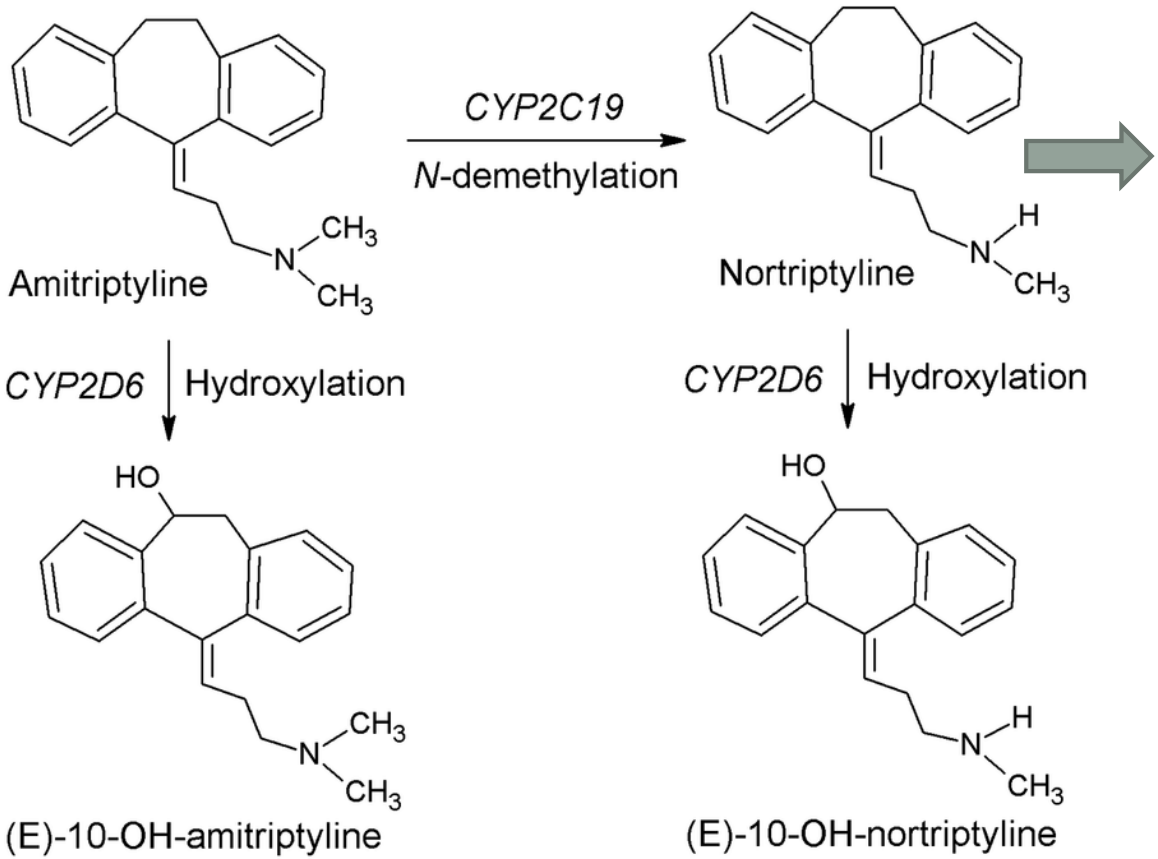
CYP = cytochrome P450; UGT2B7 = uridine diphosphate glucuronosyltransferase 2B7.



CANNABIS y ANTIDEPRESIVOS

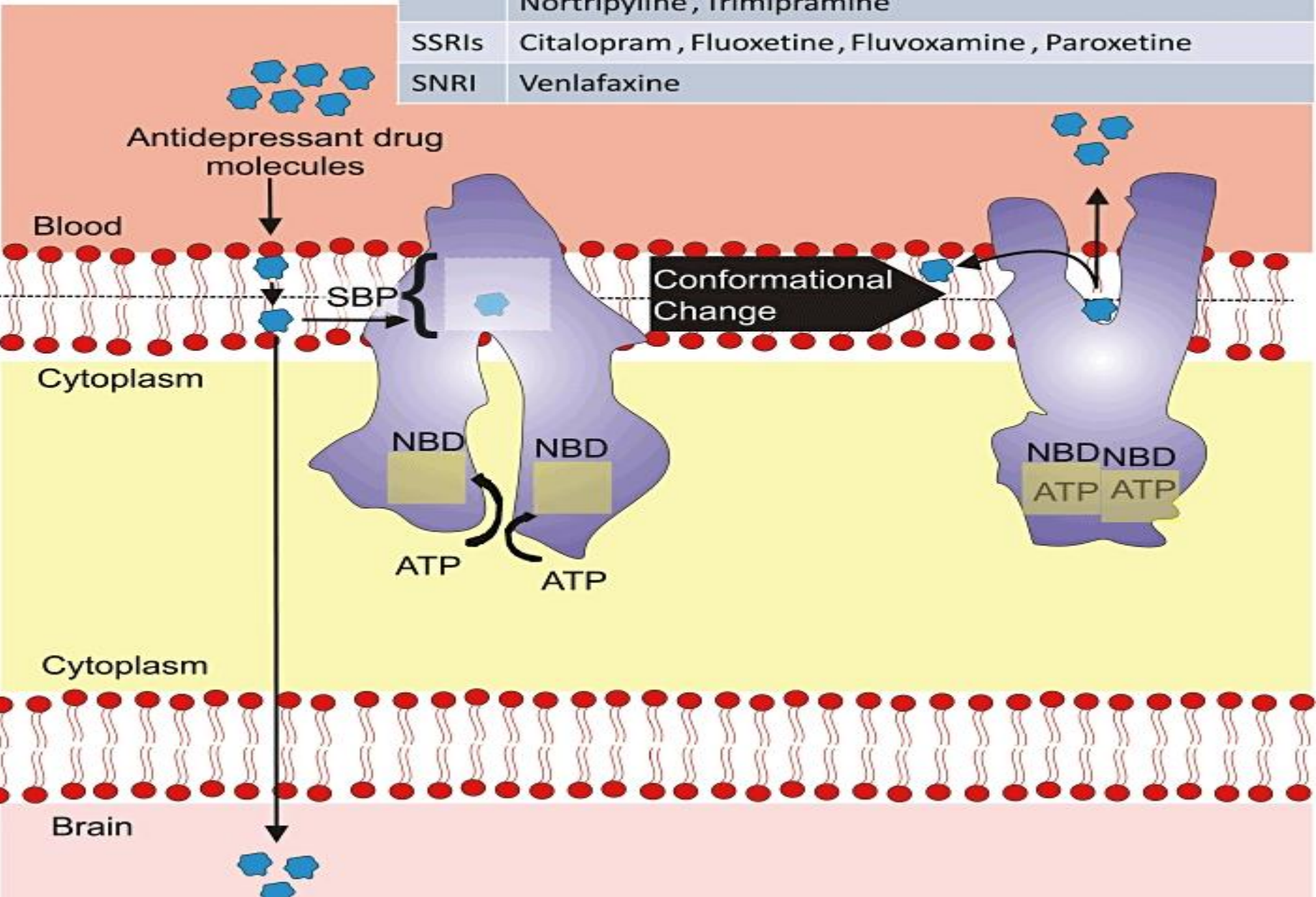
CANNABIS y ANTIDEPRESIVOS

Drug	CYP	Active metabolite
Bupropion	2B6	hydroxybupropion, threohydrobupropion, erythrohydrobupropion
Citalopram	2C19, 3A4, 2D6	desmethylcitalopram, didesmethylcitalopram, citalopram-N-oxid
Duloxetine	1A2, 2D6	none
Escitalopram	2C19, 2D6, 3A4	desmethylcitalopram, didesmethylcitalopram
Fluoxetine	2D6, 2C9, 2C19, 3A4, 2B6	norfluoxetine
Fluvoxamine	1A2, 2D6	fluvoxamine acid
Mirtazapine	3A4, 2D6, 1A2, 2B6	desmethylmirtazapine
Paroxetine	2D6, 3A4, 1A2, 2C19, 3A5	none
Sertraline	2B6, 2C19, 3A4, 2D6, 2C9	desmethylsertraline
Trazodone	3A4, 2D6	m-chlorophenylpiperazine
Venlafaxine	2D6, 3A4, 2C19	O-desmethylvenlafaxine, N-desmethylvenlafaxine

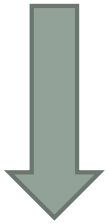


Wilens T.E., Biederman J., Spencer T.J. Case Study: Adverse effects of smoking marijuana while receiving tricyclic antidepressants. (1997) Journal of the American Academy of Child and Adolescent Psychiatry, 36 (1) , pp. 45-48.

Potential P-gp substrate antidepressants	
TCAs	Amitriptyline , Desipramine, Doxepine, Imipramine , Nortripyline , Trimipramine
SSRIs	Citalopram , Fluoxetine , Fluvoxamine , Paroxetine
SNRI	Venlafaxine

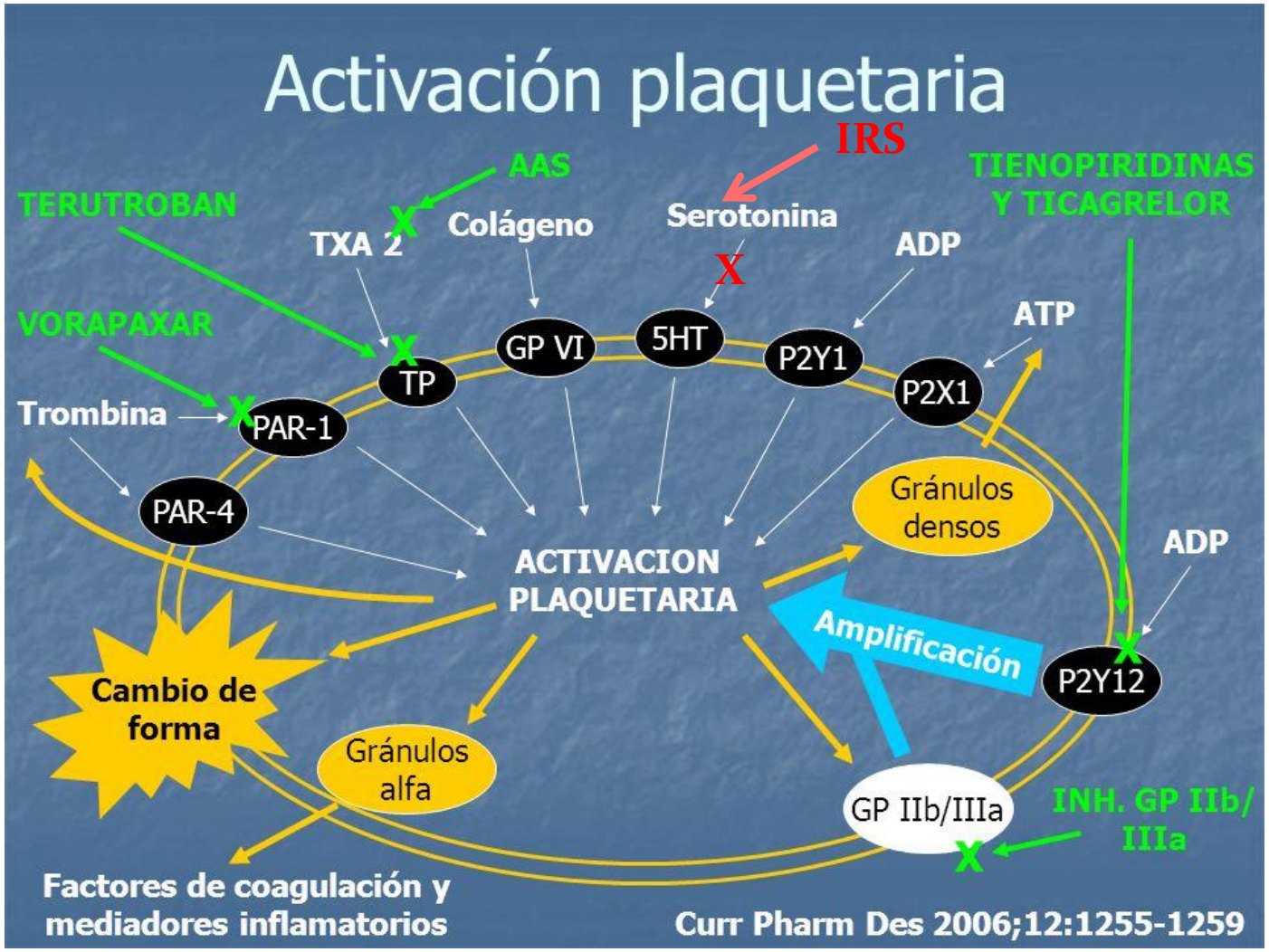


Si los cannabinoides interfieren en la eliminación de estos fármacos y/o producen una disminución en trasportadores de efflujo, el resultado sería el mismo, aumento en los niveles de antidepresivos



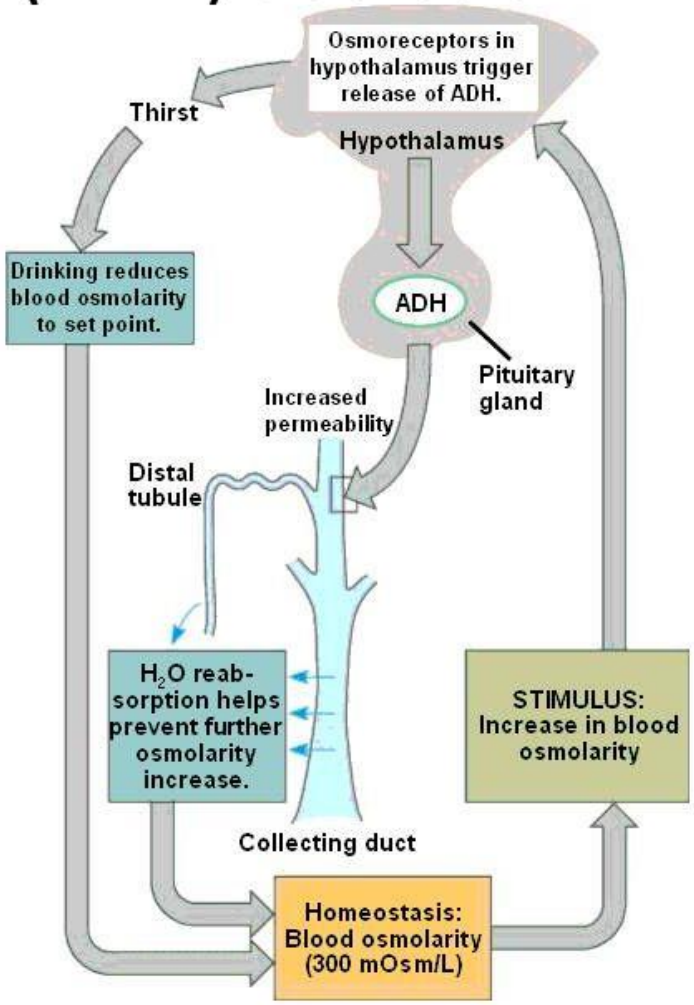
Efectos adversos

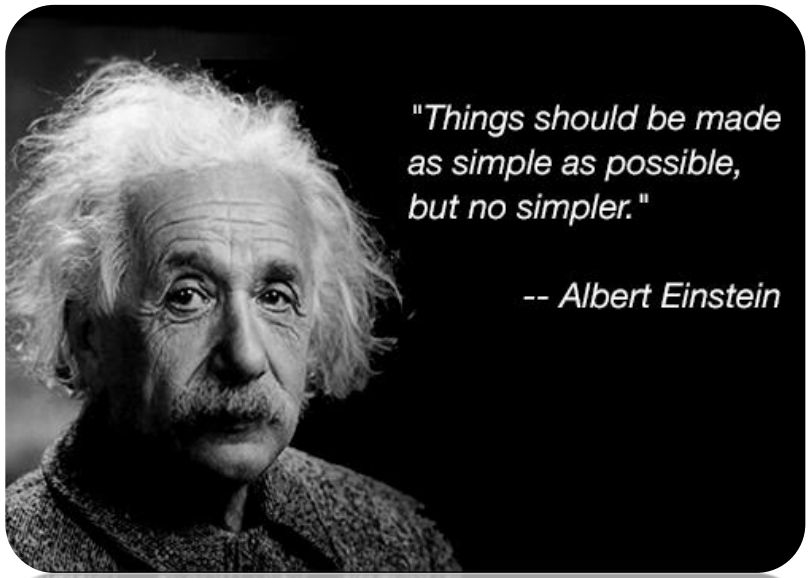
- SINDROME SEROTONINÉRGICO


Activación plaquetaria
IRS
AAS
TERUTROBAN
TXA 2
Colágeno
Serotonina
ADP
TIENOPIRIDINAS Y TICAGRELOR
VORAPAXAR
ATP
GP VI
5HT
P2Y1
TP
P2X1
Trombina
PAR-1
PAR-4
Gránulos densos
ACTIVACION PLAQUETARIA
ADP
Amplificación
P2Y12
Cambio de forma
Gránulos alfa
GP IIb/IIIa
INH. GP IIb/ IIIa
Factores de coagulación y mediadores inflamatorios
Curr Pharm Des 2006;12:1255-1259

Antidiuretic Hormone (ADH) Secretion

- Controls how much water is reabsorbed from the collecting duct back into the bloodstream.
  - If ADH **is** secreted, the collecting duct becomes permeable to water & water leaves by way of osmosis into the highly hypertonic medulla of the kidney.
  - Water is then reabsorbed back into the bloodstream
  - If ADH is **not** secreted, the collecting duct remains impermeable to water
  - Urine will then contain a high amount of water.





MUCHAS GRACIAS