10th International Association of Physical Chemists (IAPC) Meeting: Joint World Conferences on Physico Chemical Methods in Drug Discovery and Development and on ADMET and DMPK, Belgrade, Serbia, September 04-06, 2023

Neuropharmacokinetics: the secret life of - old and novel - psychopharmacological drugs

Miroslav M. Savić

University of Belgrade – Faculty of Pharmacy

Belgrade, Serbia

Acknowledgement

- Parts of the presented research were funded by:

- Science Fund of the Republic of Serbia, Grant No 7749108, Neuroimmune aspects of mood, anxiety and cognitive effects of leads/drug candidates acting at GABAA and/or sigma-2 receptors: In vitro/in vivo delineation by nano- and hiPSC-based platform – NanoCellEmoCog

- Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 821528 (NeuroDeRisk: Neurotoxicity De-Risking in Preclinical Drug Discovery). This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and the European Federation of Pharmaceutical Industries and Associations (EFPIA)

DISCLAIMER

- None of the **statements contained** in this presentation, not otherwise referenced, constitutes the official policy of any agency or government official, but is a scientific/professional opinion of MMS, **not directly affected**

A. either by **professional engagement** of MMS **in the public health system of Serbia**, in terms of regulation of registration and clinical trials of medicines (full-member of the Commission for registration of human medicines of the Medicines and Medical Devices Agency of Serbia since 2014; Full-member of the Ethics Committee of Republic of Serbia since 2019),

B. or by **engagement** of MMS **in drug discovery and development**, exemplified by co-authored patents (WO2016196961 Ligands selective to alpha6 subunit-containing GABAA receptors and their methods of use; WO2017161370 Treatment of cognitive and mood symptoms in neurodegenerative and neuropsychiatric disorders with alpha5-containing GABAA receptor agonists)

NEEDS for NOVEL TREATMENTS IN CNS DISORDERS ARE HIGH…

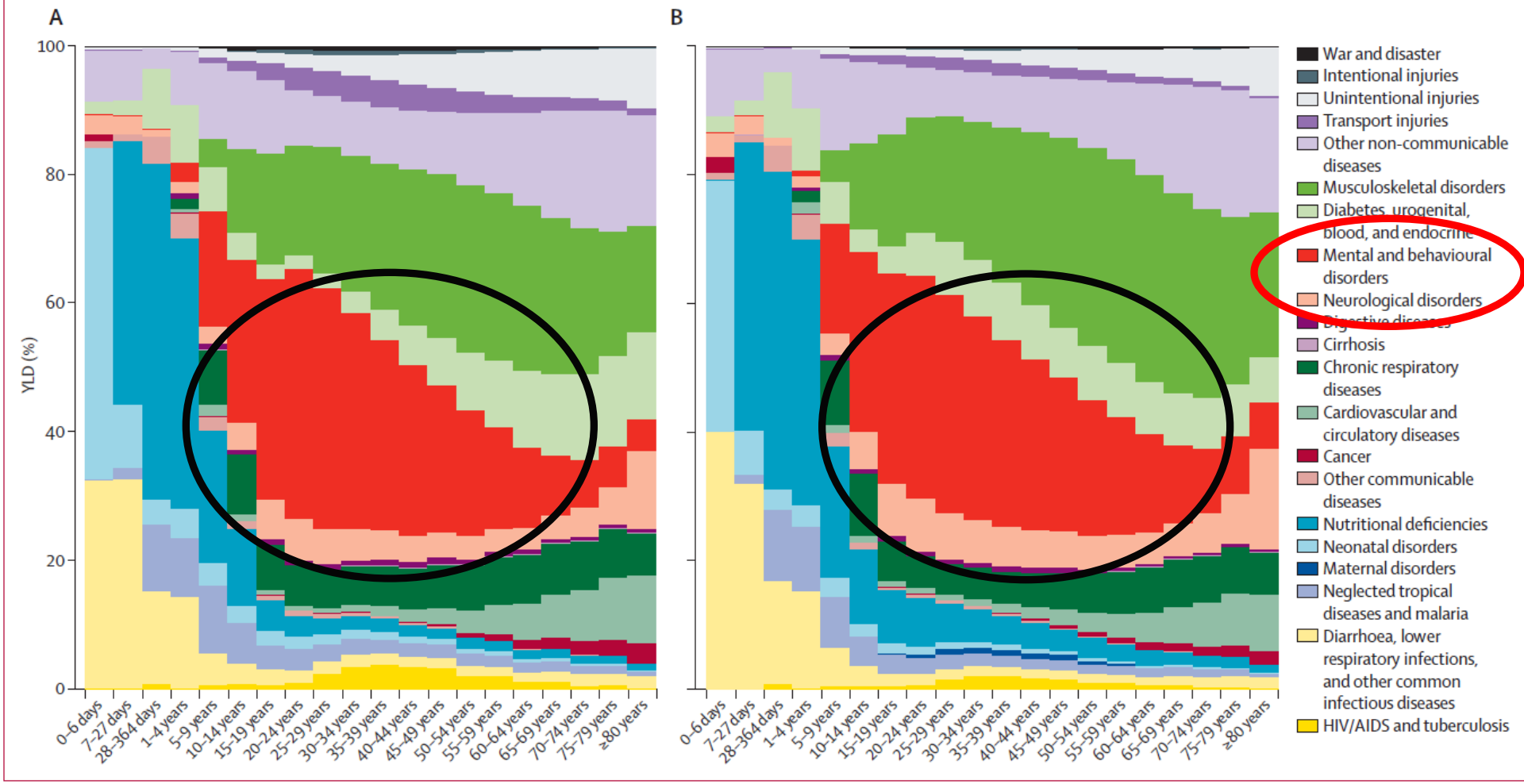
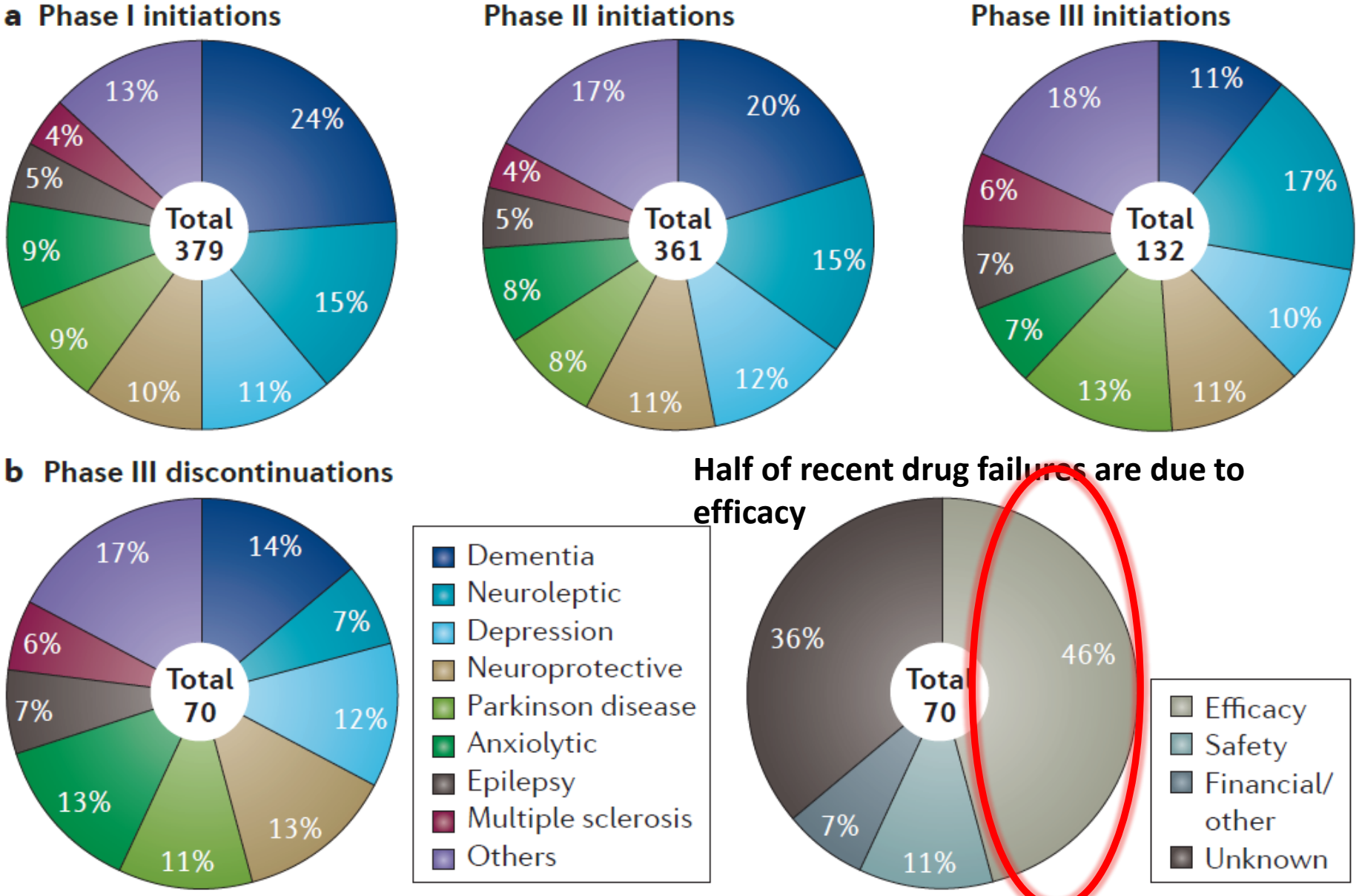


Figure 2: Percentage of years lived with disability (YLDs) in 2010, by cause and age
(A) In male individuals. (B) In female individuals. An interactive version of this figure is available online at http://healthmetricsandevaluation.org/gbd/visualizations/regional.

Kesselheim AS, Hwang TJ, Franklin JM. Two decades of new drug development for central nervous system disorders. Nat Rev Drug Discov. 2015 Dec;14(12):815-6.



Kesselheim AS, Hwang TJ, Franklin JM. Two decades of new drug development for central nervous system disorders. Nat Rev Drug Discov. 2015 Dec;14(12):815-6.

Butlen-Ducuing F, Pétavy F, Guizzaro L, Zienowicz M, Haas M, Alteri E, Salmonson T, Corruble E. Regulatory watch: Challenges in drug development for central nervous system disorders: a European Medicines Agency perspective. Nat Rev Drug Discov. 2016 Nov 29;15(12):813-814. doi: 10.1038/nrd.2016.237 .

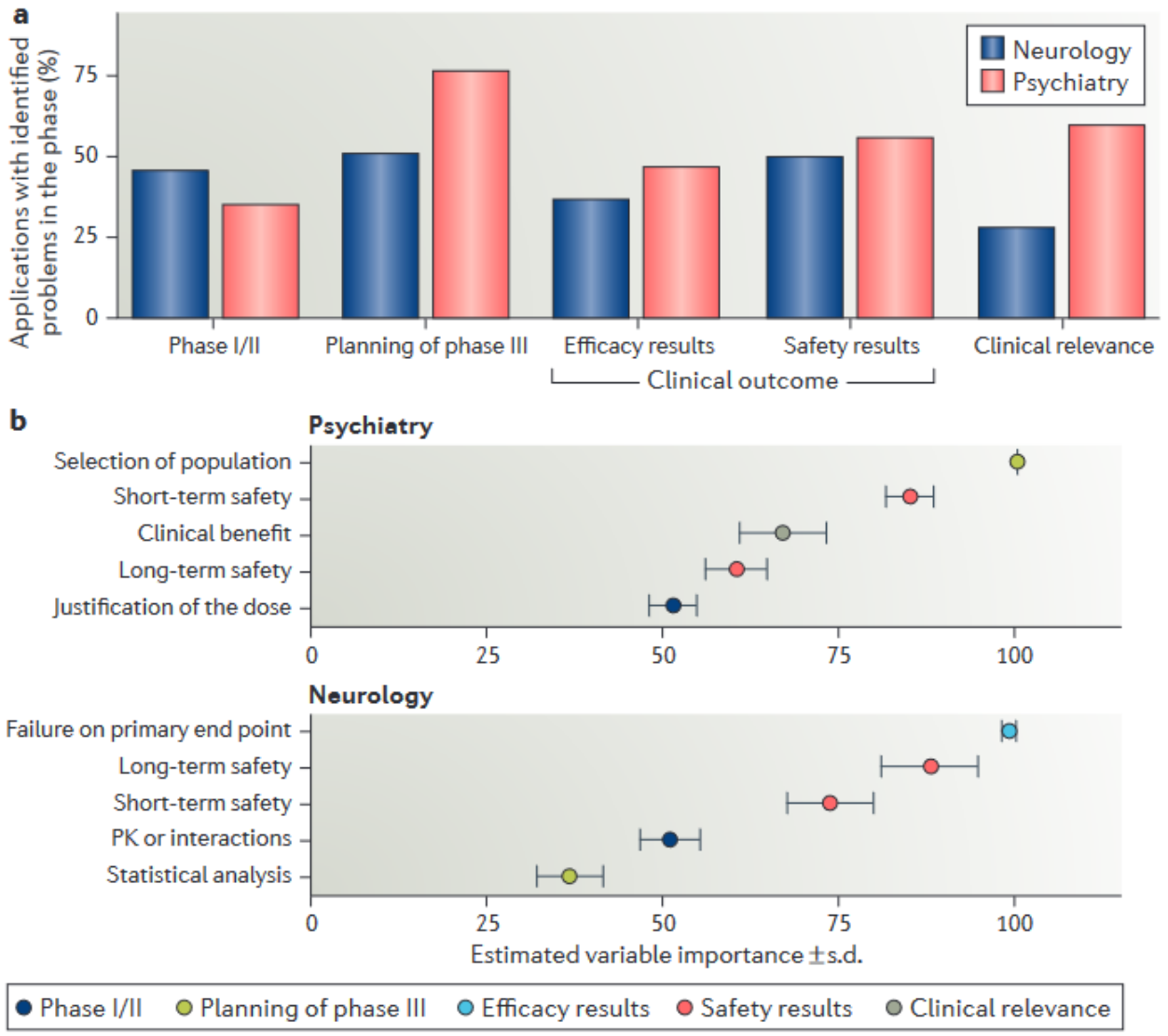
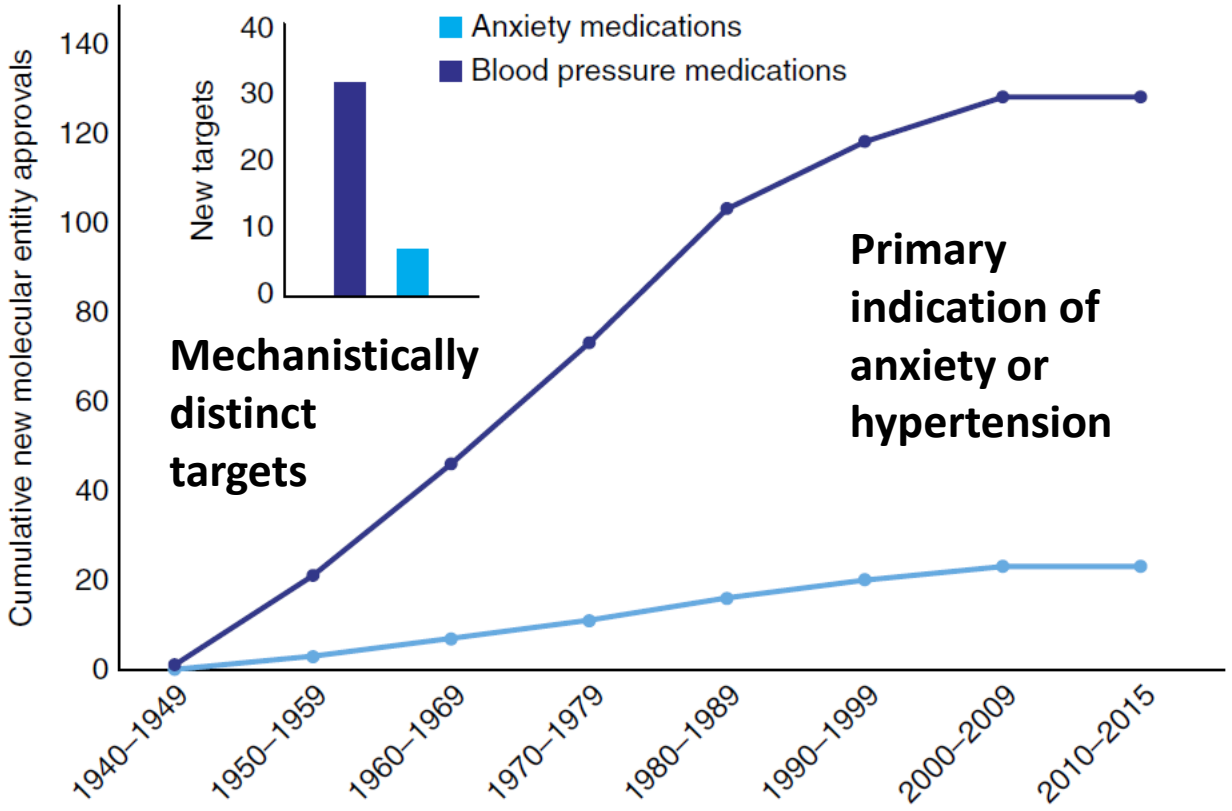


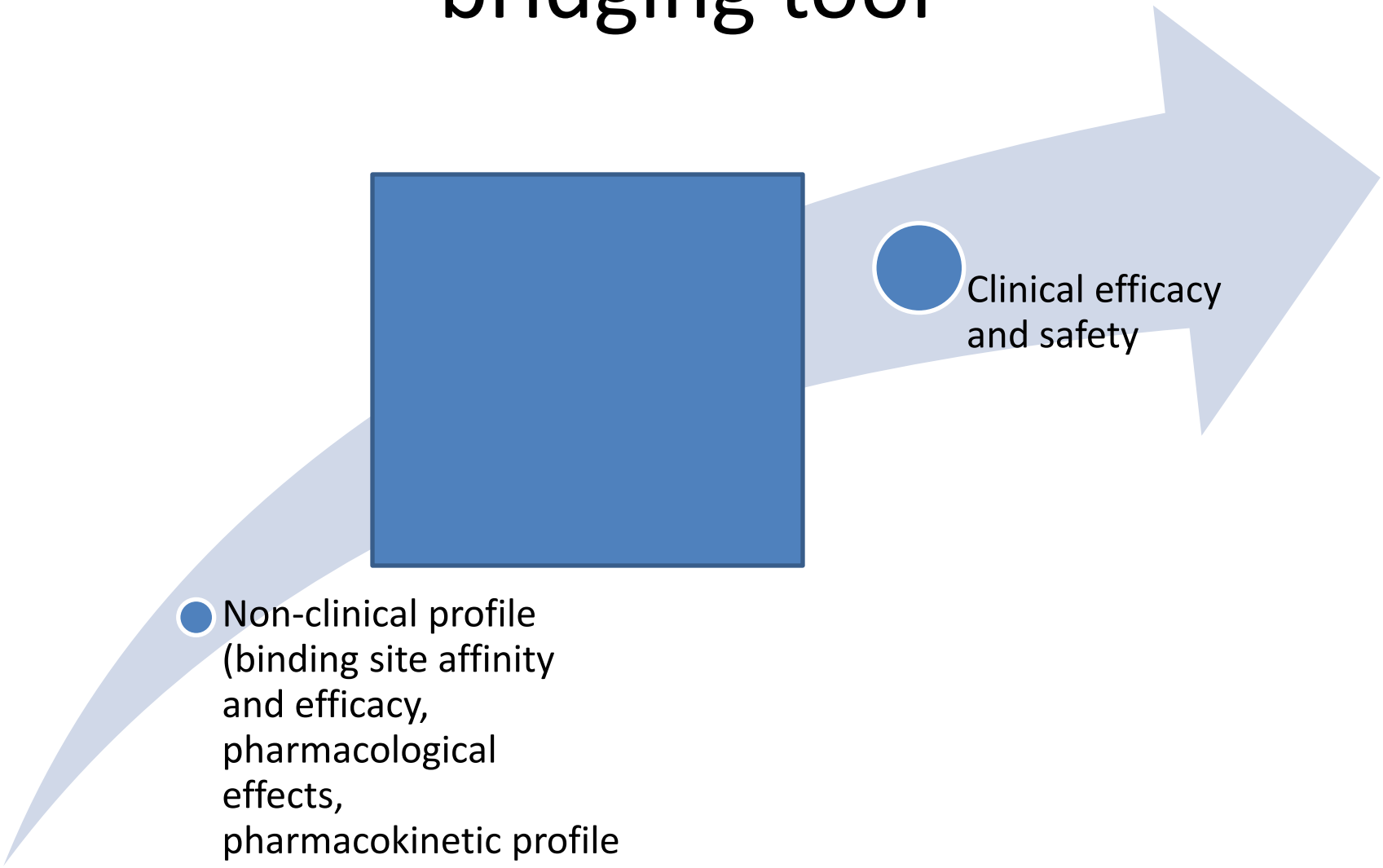
Figure 1| **Issues with clinical development programmes of products for psychiatry or neurology indications reviewed by the European Medicines Agency between 1995 and 2014. a** | The nature of major issues overall. **b** | The estimated importance of the five issues that had the strongest impact on the outcome for psychiatry and neurology applications. See Supplementary information S1 (box) for further details. PK, pharmacokinetics; s.d., standard deviation.

Few new pharmacotherapies for the treatment of anxiety have been developed since the 1940s



Calhoon GG, Tye KM. Resolving the neural circuits of anxiety. Nat Neurosci. 2015;18(10):1394-404

Neuropharmacokinetics as a bridging tool



Neuropharmacokinetics

Око 647 резултата (**0,08** сек)

Novel CNS drug discovery and development approach: model-based integration to predict **neuro-pharmacokinetics** and pharmacodynamics
ECM de Lange, W van den Brink… - Expert Opinion on …, 2017 - Taylor & Francis
Introduction: CNS drug development has been hampered by inadequate consideration of CNS pharmacokinetic (PK), pharmacodynamics (PD) and disease complexity (reductionist …
☆ Сачувај 99 Цитирај 50 пута наведен Сродни чланци Све верзије (12)

The **neuropharmacokinetics** of temozolomide in patients with resectable brain tumors: potential implications for the current approach to chemoradiation
J Portnow, B Badie, M Chen, A Liu, S Blanchard… - Clinical Cancer …, 2009 - AACR
Purpose: Intracerebral microdialysis (ICMD) is an accepted method for monitoring changes in neurochemistry from acute brain injury. The goal of this pilot study was to determine the …
☆ Сачувај 99 Цитирај 238 пута наведен Сродни чланци Све верзије (6)

[HTML] Evaluation of the route dependency of the pharmacokinetics and **neuro-pharmacokinetics** of tramadol and its main metabolites in rats
B Sheikholeslami, M Gholami, H Lavasani… - European Journal of …, 2016 - Elsevier
… on the observed similarities in tramadol metabolism and transport between humans and rats, the results of this study may be used for initial predictions of the **neuropharmacokinetics** of …
☆ Сачувај 99 Цитирај 19 пута наведен Сродни чланци Све верзије (6)

Microdialysis study of the **neuropharmacokinetics** of phenytoin in rat hippocampus and frontal cortex
MC Walker, MS Alavijeh, SD Shorvon, PN Patsalos - Epilepsia, 1996 - Wiley Online Library
… known about the **neuropharmacokinetics** of PHT in brain extracellular fluid (ECF), the pharmacodynamically relevant compartment. To characterize the **neuropharmacokinetics** of brain …
☆ Сачувај 99 Цитирај 46 пута наведен Сродни чланци Све верзије (7)

[HTML] **Neuropharmacokinetics**: a bridging tool between CNS drug development

neuropharmacokinetics of morphine and morphine-6-β-d-glucuronide
F Bourasset, JM Scherrmann - Life sciences, 2006 - Elsevier
We investigated whether capacity-limited transport processes were involved in morphine and morphine-6-β-d-glucuronide (M6G) **neuropharmacokinetics**, at the level of the blood–brain …
☆ Сачувај 99 Цитирај 33 пута наведен Сродни чланци Све верзије (8)

Neuropharmacokinetics of a new α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (ampa) modulator, S18986 [(S)-2, 3-dihydro-[3, 4] cyclopentano-1, 2, 4 …
F Bourasset, K Bernard, C Muñoz, P Genissel… - Drug metabolism and …, 2005 - ASPET
The aim of our study was to determine the **neuropharmacokinetics** of S18986 [(S)-2,3-dihydro-[3,4]cyclo benzothiadiazine-1,1-dioxide], a new positive allosteric modulator …
☆ Сачувај 99 Цитирај 29 пута наведен Сродни чланци Све верзије (12)

Antiepileptic drug pharmacokinetics and **neuropharmacokinetics** in individual rats by repetitive withdrawal of blood and cerebrospinal fluid: phenytoin
YI Lolin, N Ratnaraj, M Hjelm, PN Patsalos - Epilepsy research, 1994 - Elsevier
The temporal pharmacokinetic (blood) and neurophannacokinetic (cerebrospinal fluid, CSF) interrelationship of phenytoin was studied after acute and during chronic (up to 5 days) …
☆ Сачувај 99 Цитирај 35 пута наведен Сродни чланци Све верзије (6)

… and behaving rat model for the chronic and simultaneous study of drug pharmacokinetics (blood) and **neuropharmacokinetics** (cerebrospinal fluid): hematological and …
PN Patsalos, MS Alavijeh, J Semba, YI Lolin - Journal of pharmacological …, 1992 - Elsevier
A freely moving and behaving rat model for the chronic and simultaneous study of drug pharmacokinetics (blood) and **neuropharmacokinetics** [cerebrospinal fluid (CSF)] is described. …
☆ Сачувај 99 Цитирај 40 пута наведен Сродни чланци Све верзије (7)

Local tetanus in cats: **Neuropharmacokinetics** of ^{125}I-tetanus toxin
HH Wellhöner, B Hensel, UC Seib - Naunyn-Schmiedeberg's Archives of …, 1973 - Springer

0090-9556/06/3402-318–323$20.00
DRUG METABOLISM AND DISPOSITION

DMD 34:318–323, 2006

Vol. 34, No. 2
7211/3083197
Printed in U.S.A.

DRUG METABOLISM & DISPOSITION

BRAIN DISTRIBUTION OF CETIRIZINE ENANTIOMERS: COMPARISON OF THREE DIFFERENT TISSUE-TO-PLASMA PARTITION COEFFICIENTS: K_p, $K_{p,u}$, AND $K_{p,uu}$

Anubha Gupta, Pierre Chatelain, Roy Massingham, E. Niclas Jonsson, and Margareta Hammarlund-Udenaes

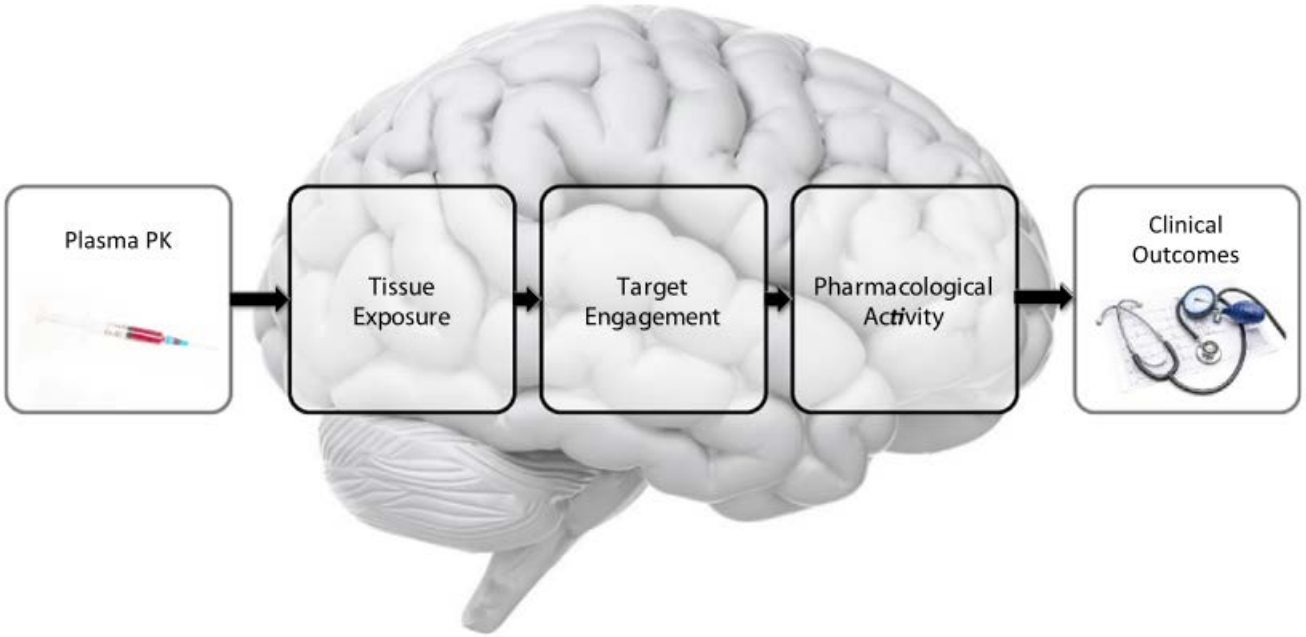
Division of Pharmacokinetics and Drug Therapy, Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden (A.G., E.N.J., M.H.U.); and UCB Société Anonyme, Braine-l'Alleud, Belgium (P.C., R.M.)

Received September 5, 2005; accepted November 18, 2005

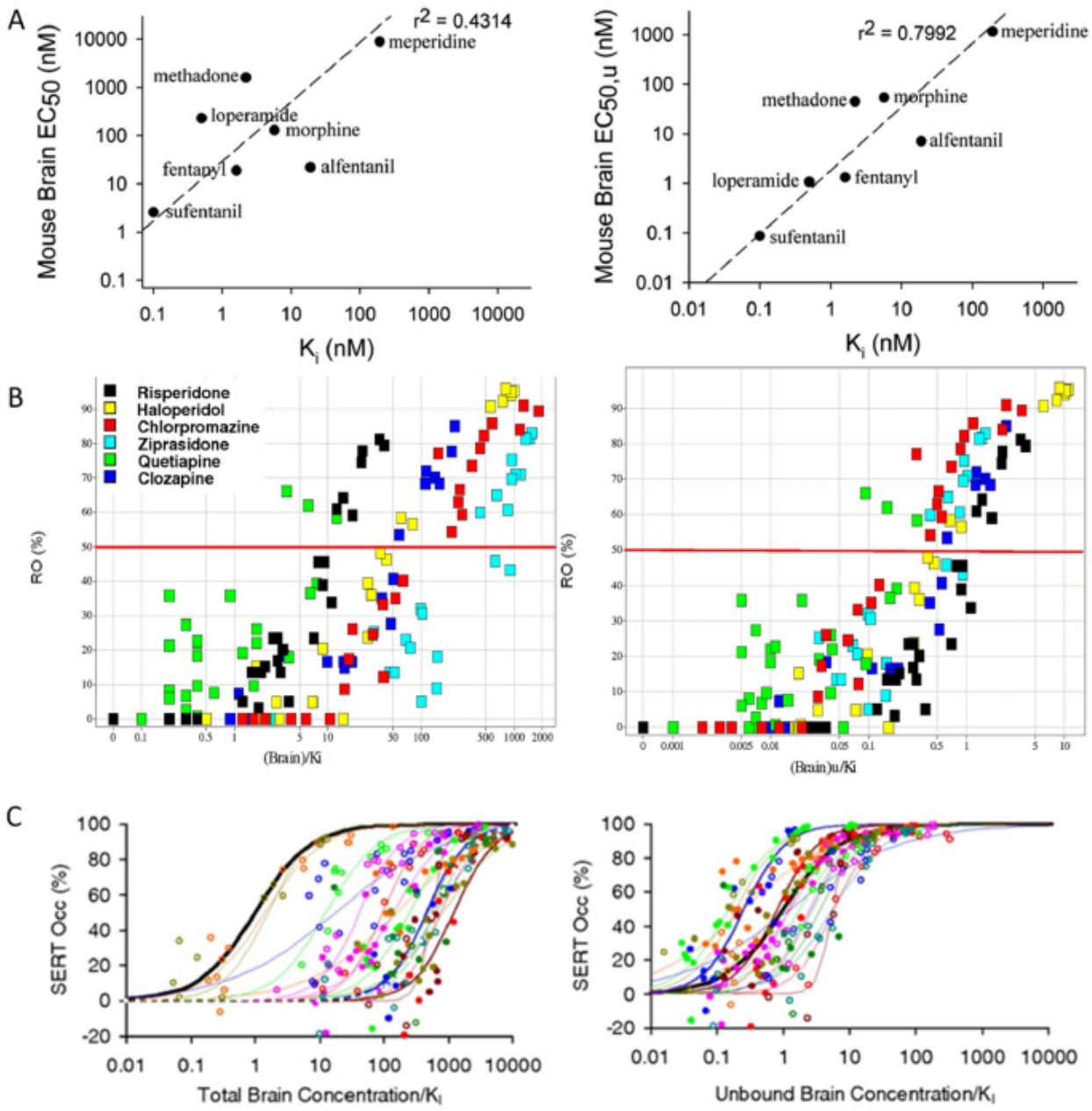
ABSTRACT:

The objective of this study was to compare the blood-brain barrier (BBB) transport and brain distribution of levo- (*R*-CZE) and dextrocetirizine (*S*-CZE). Microdialysis probes, calibrated using retrodialysis by drug, were placed into the frontal cortex and right jugular vein of eight guinea pigs. Racemic CZE (2.7 mg/kg) was administered as a 60-min i.v. infusion. Unbound and total concentrations of the enantiomers were measured in blood and brain with liquid chromatography-tandem mass spectrometry. The brain distribution of the CZE enantiomers were compared using the parameters K_p, $K_{p,u}$, $K_{p,uu}$, and $V_{u,br}$. K_p compares total brain concentration to total plasma concentration, $K_{p,u}$ compensates for binding in plasma, whereas $K_{p,uu}$ also compensates for binding within the brain tissue and directly quantifies the transport across the BBB. $V_{u,br}$ describes binding within the brain. The stereoselective brain distribution indicated by the K_p of 0.22 and 0.04 for *S*- and *R*-CZE, respectively, was caused by different binding to plasma proteins. The transport of the CZE enantiomers across the BBB was not stereoselective, since the $K_{p,uu}$ was 0.17 and 0.14 (N.S.) for *S*- and *R*-CZE, respectively. The $K_{p,uu}$ values show that the enantiomers are effluxed to a large extent across the BBB. The $V_{u,br}$ of approximately 2.5 ml/g brain was also similar for both the enantiomers, and the value indicates high binding to brain tissue. Thus, when determining stereoselectivity in brain distribution, it is important to study all factors governing this distribution, binding in blood and brain, and the BBB equilibrium.

- the unbound (free) concentration of a drug at the site of action, such as the brain, is the driving force for pharmacological response



Gunn RN, Rabiner EA. Imaging in Central Nervous System Drug Discovery. Semin Nucl Med. 2017 Jan;47(1):89-98. doi: 10.1053/j.semnuclmed.2016.09.001. Epub 2016 Oct 28. PMID: 27987561.



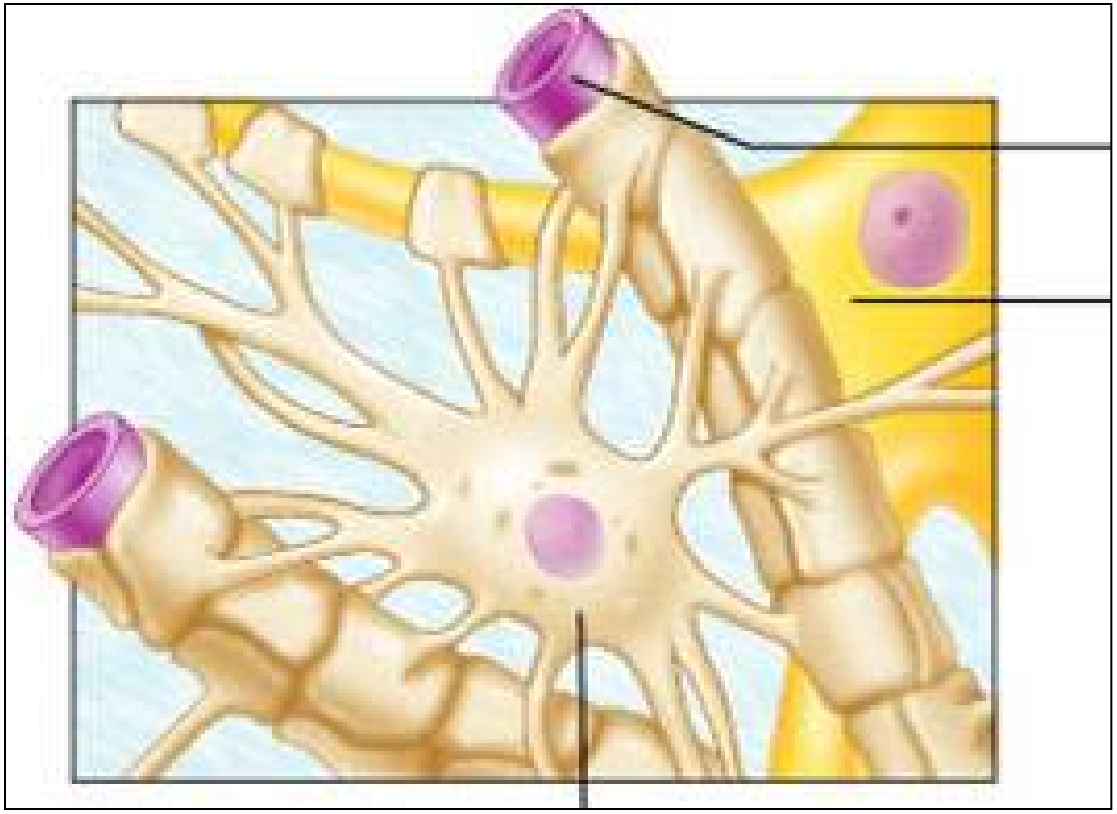
Loryan I, Reichel A, Feng B, Bundgaard C, Shaffer C, Kalvass C, Bednarczyk D, Morrison D, Lesuisse D, Hoppe E, Terstappen GC, Fischer H, Di L, Colclough N, Summerfield S, Buckley ST, Maurer TS, Fridén M. Unbound Brain-to-Plasma Partition Coefficient, $K_{p,uu,brain}$-a Game Changing Parameter for CNS Drug Discovery and Development. Pharm Res. 2022 Jul;39(7):1321-1341. doi: 10.1007/s11095-022-03246-6.

https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?tab=biology&ligandId=38

Affinity profile of clozapine

Target	Sp.	Type	Action	Value	Parameter	Reference
H_1 receptor	Hs	Antagonist	Antagonist	8.8 – 9.6	pK_i	5,16,31
5-HT_{2A} receptor	Rn	Antagonist	Inverse agonist	8.9	pK_i	6
5-HT_{2B} receptor	Hs	Antagonist	Antagonist	8.0 – 8.8	pK_i	11,23,42
5-HT_{2A} receptor	Hs	Antagonist	Inverse agonist	7.6 – 9.0	pK_i	11,16,23,31,41
α_{1B}-adrenoceptor	Hs	Antagonist	Antagonist	8.2	pK_i	43
α_{1A}-adrenoceptor	Hs	Antagonist	Antagonist	8.1	pK_i	43
5-HT_{2C} receptor	Hs	Antagonist	Inverse agonist	7.4 – 8.7	pK_i	7,10-11,16,23,41
5-HT_6 receptor	Hs	Antagonist	Inverse agonist	7.8 – 8.1	pK_i	1,4,13,27
5-HT_6 receptor	Rn	Antagonist	Inverse agonist	7.5 – 8.4	pK_i	2-4,14,23-24,29
5-HT_7 receptor	Rn	Antagonist	Inverse agonist	7.2 – 8.2	pK_i	14,29-30,33
α_{1D}-adrenoceptor	Hs	Antagonist	Antagonist	7.7	pK_i	43
5-HT_7 receptor	Hs	Antagonist	Inverse agonist	7.2 – 7.8	pK_i	15,27,40
D_4 receptor	Hs	Antagonist	Antagonist	7.5	pK_i	17
5-HT_7 receptor	Mm	Antagonist	Inverse agonist	7.4	pK_i	26
5-HT_{1F} receptor	Hs	Agonist	Full agonist	6.9	pK_i	31
D_1 receptor	Hs	Antagonist	Antagonist	6.9	pK_i	37
5-HT_{1A} receptor	Hs	Agonist	Full agonist	6.8 – 6.9	pK_i	23,25,31
D_5 receptor	Hs	Antagonist	Antagonist	6.6	pK_i	37
H_4 receptor	Hs	Antagonist	Antagonist	6.2 – 6.7	pK_i	18-20,44
5-HT_{1D} receptor	Hs	Agonist	Full agonist	6.4	pK_i	31
5-ht_{1e} receptor	Hs	Agonist	Full agonist	6.4	pK_i	31
D_2 receptor	Hs	Antagonist	Antagonist	5.8 – 6.9	pK_i	8,22,32,34,39
5-HT_{5A} receptor	Hs	Antagonist	Antagonist	6.0 – 6.5	pK_i	9,28
5-HT_{1B} receptor	Hs	Agonist	Full agonist	6.2	pK_i	31
D_2 receptor	Rn	Antagonist	Antagonist	6.2	pK_i	35
H_3 receptor	Rn	Antagonist	Antagonist	5.8	pK_i	21
D_3 receptor	Hs	Antagonist	Antagonist	5.2 – 6.3	pK_i	8,34
D_3 receptor	Rn	Antagonist	Antagonist	5.7	pK_i	35
H_4 receptor	Rn	Antagonist	Antagonist	5.7	pK_i	20
H_4 receptor	Mm	Antagonist	Antagonist	5.5	pK_i	20
5-HT_{5A} receptor	Mm	Antagonist	Antagonist	5.3	pK_i	9
M_1 receptor	Hs	Allosteric modulator	Positive	7.9	pIC_{50}	38

The blood-brain barrier



Capillary wall made of microvascular endothelial cells

Neuron

Astrocyte

An endothelial barrier formed by the blood vessels that vascularize the parenchyma of the CNS. The BBB makes up most of the surface area of the brain barriers and hence is most important for drug delivery to the CNS

Ilić T, Đoković JB, Nikolić I, Mitrović JR, Pantelić I, Savić SD, Savić MM. Parenteral Lipid-Based Nanoparticles for CNS Disorders: Integrating Various Facets of Preclinical Evaluation towards More Effective Clinical Translation. Pharmaceutics. 2023 Jan 29;15(2):443. doi: 10.3390/pharmaceutics15020443.

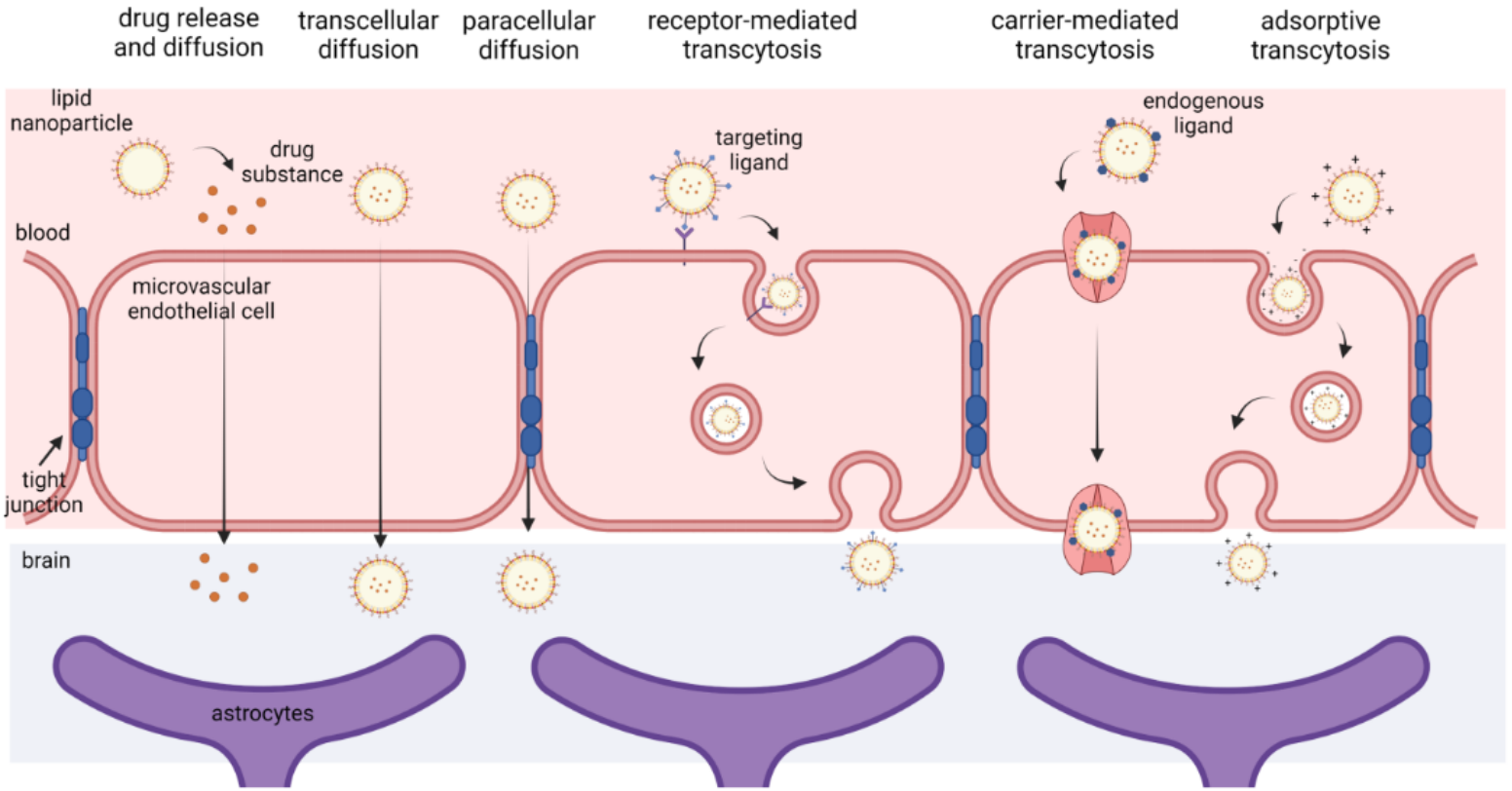


Figure 3. Proposed drug-delivery mechanisms across BBB in interaction with lipid nanoparticles [5,10,54,140]. Created with BioRender.com (accessed on 16 February 2022).

The presence of the BBB readily leads to an asymmetry of drug (unbound) exposure in the brain and in the systemic circulation, which prohibits the use of unbound drug concentration in plasma as a surrogate for unbound drug concentration in the brain

Neuropharmacokinetic parameters

- brain-to-plasma partition coefficient:

Kp = AUC0–t, brain/AUC0–t, plasma

- The concept of $K_{p,uu,brain}$, describing the ratio of unbound drug concentrations in brain interstitial fluid to that of unbound drug concentrations in blood (or plasma), was introduced in: Gupta A, et al. Brain distribution of cetirizine enantiomers: **comparison of three different tissue-to-plasma partition coefficients: K(p), K(p,u), and K(p,uu)**. Drug Metab Dispos. 2006 Feb;34(2):318-23.
- Kp,uu can be calculated by dividing either

a) the area under the curve (AUC) of the profile of the concentration of unbound drug in brain and plasma after a single administration or

b) the steady-state unbound concentrations of drug in brain interstitial fluid and plasma

Ligands that selectively potentiate GABAA receptors containing the α6 subunit

Journal of Medicinal Chemistry

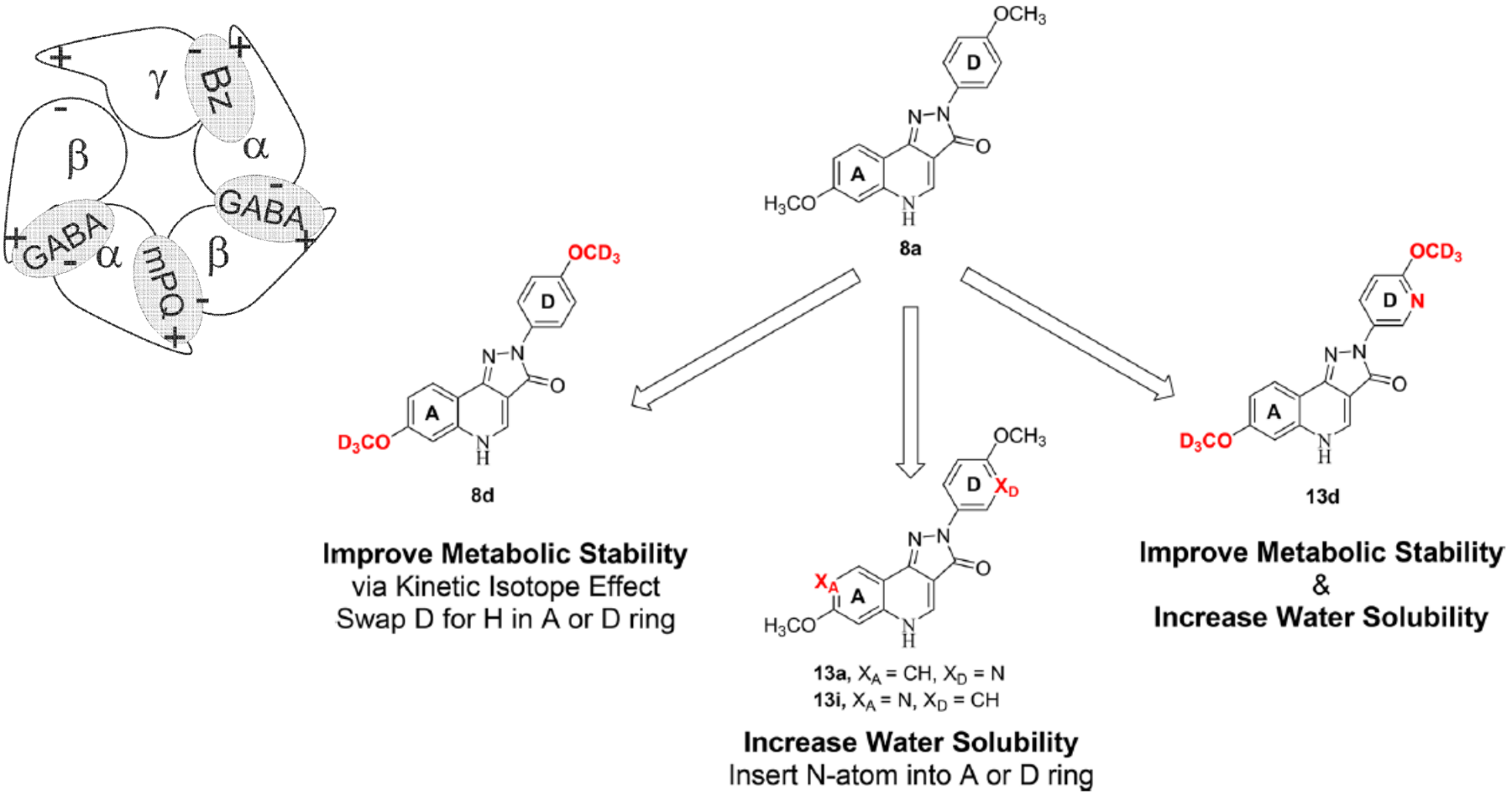
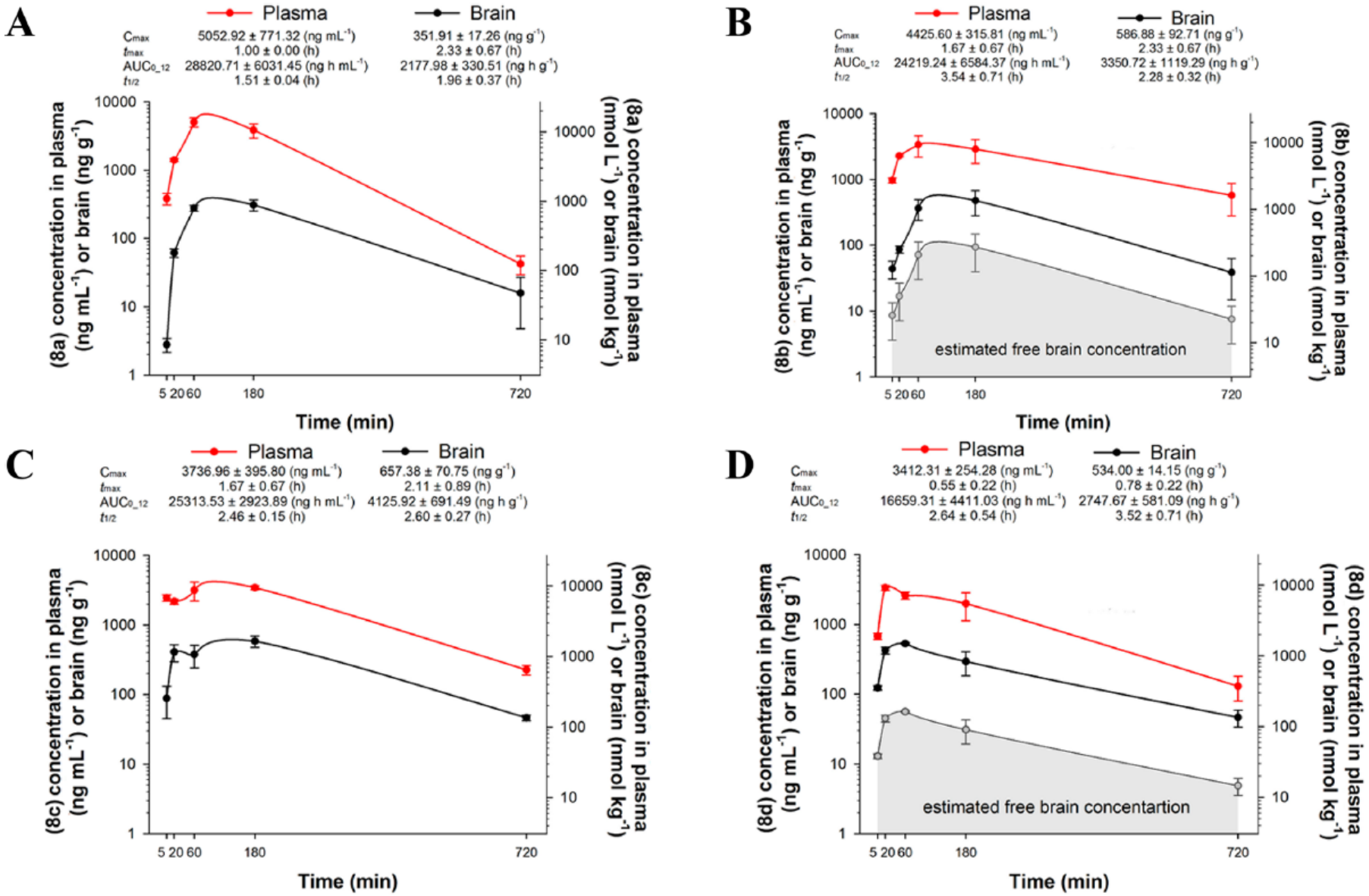


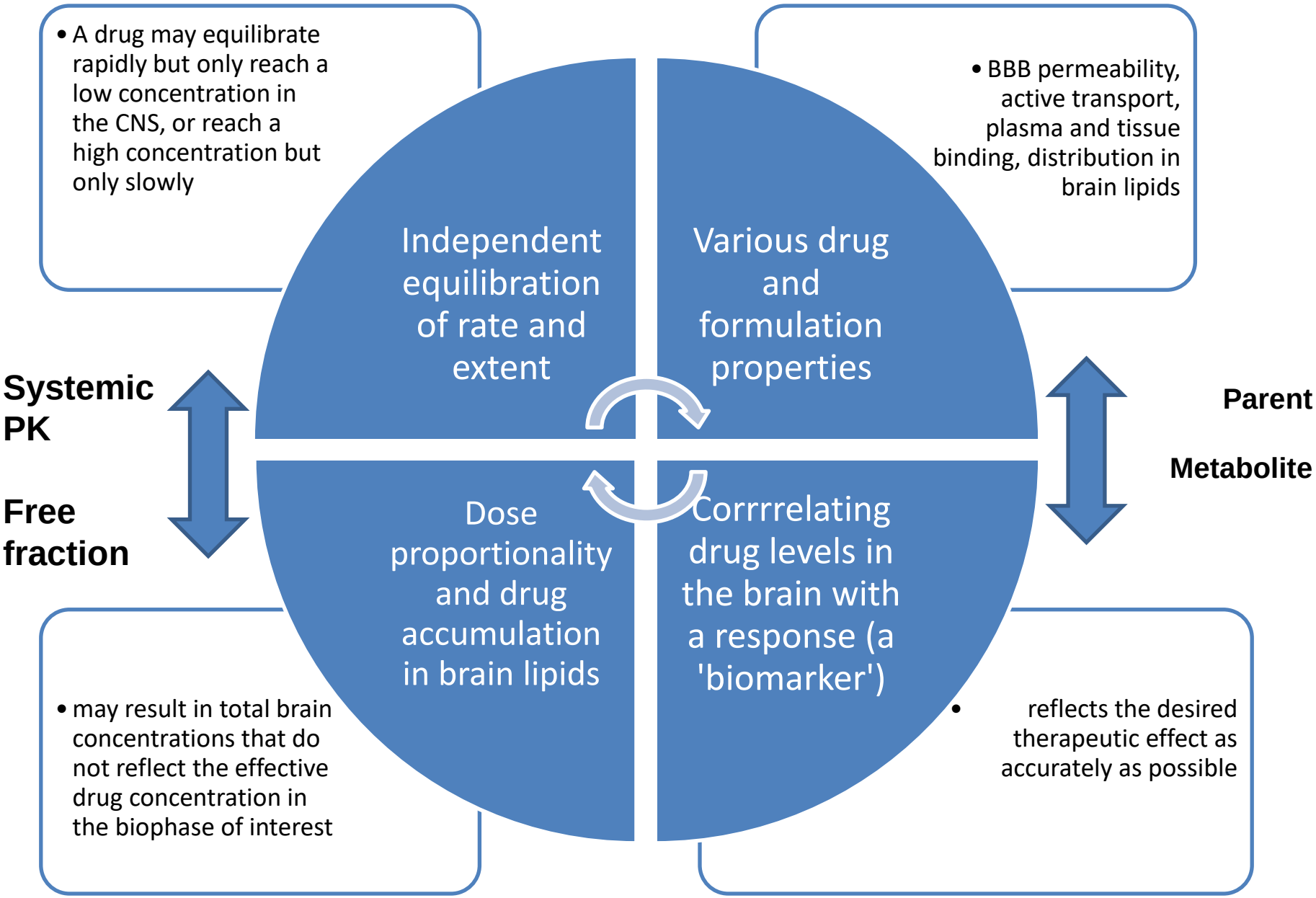
Figure 3. General strategy of this work to improve the bioavailability of the ligands.

Knutson DE, Kodali R, Divović B, Treven M, Stephen MR, Zahn NM, Dobričić V, Huber AT, Meirelles MA, Verma RS, Wimmer L, Witzigmann C, Arnold LA, Chiou LC, Ernst M, Mihovilovic MD, Savić MM, Sieghart W, Cook JM. J Med Chem. 2018 Mar 22;61(6):2422-2446.

Knutson DE, Kodali R, Divović B, Treven M, Stephen MR, Zahn NM, Dobričić V, Huber AT, Meirelles MA, Verma RS, Wimmer L, Witzigmann C, Arnold LA, Chiou LC, Ernst M, Mihovilovic MD, Savić MM, Sieghart W, Cook JM. Design and Synthesis of Novel Deuterated Ligands Functionally Selective for the γ-Aminobutyric Acid Type A Receptor ($GABA_AR$) α6 Subtype with Improved Metabolic Stability and Enhanced Bioavailability. J Med Chem. 2018 Mar 22;61(6):2422-2446. doi: 10.1021/acs.jmedchem.7b01664.



Processes and factors affecting and stemming from neuropharmacokinetic behavior



Bernardo A, Lee P, Marcotte M, Mian MY, Rezvanian S, Sharmin D, Kovačević A, Savić MM, Cook JM, Sibille E, Prevot TD. Symptomatic and neurotrophic effects of GABAA receptor positive allosteric modulation in a mouse model of chronic stress. Neuropsychopharmacology. 2022 Aug;47(9):1608-1619. doi: 10.1038/s41386-022-01360-y.

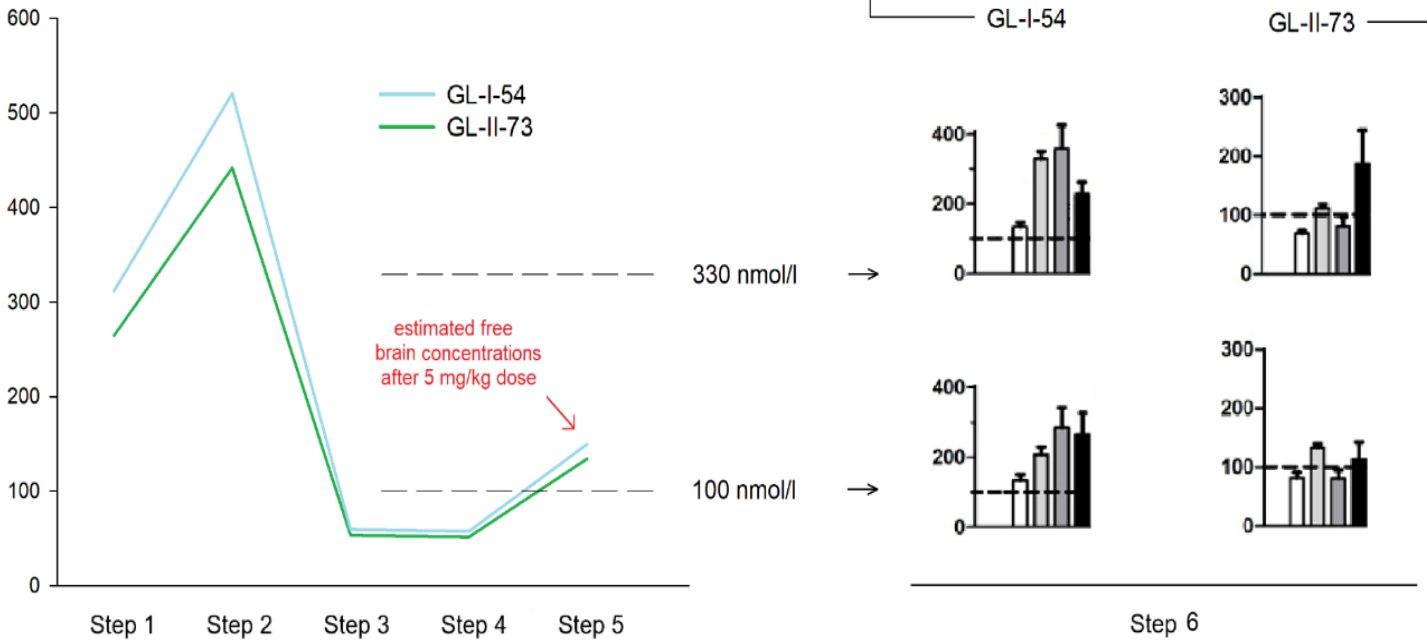
3 mg/kg	5 mg/kg (estimation)			
brain concentration				
total		free		
ng/g			ng/ml	nmol/l
311.75	520.62	59.82	57.52	148.98
264.61	441.90	53.65	51.59	133.62
/	x1.67	xFF	/1.04	x2.59
Step 1	Step 2	Step 3	Step 4	Step 5

% response to GABA alone							
α_1		α_2		α_3		α_5	
100	330	100	330	100	330	100	330
+	+	++	+++	+++	+++	+++	++
Ø	Ø	+	Ø	Ø	Ø	Ø	++
Ø < 120%		+ < 200%		++ < 250%		+++ ≥ 250%	
Step 6							

estimated range of potentiation of $GABA_A$ receptors after 5 mg/kg dose

GL-I-54

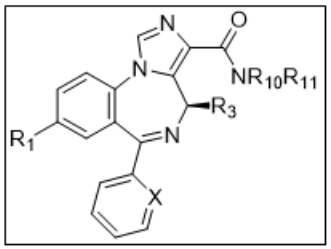
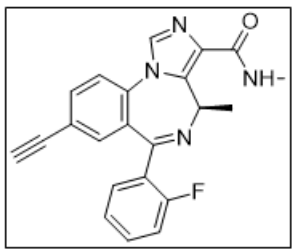
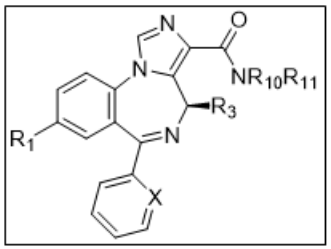
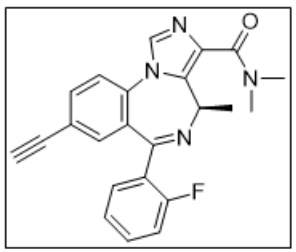
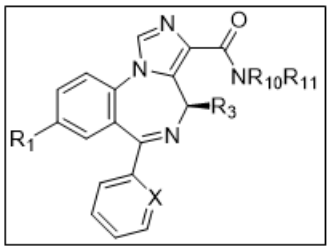
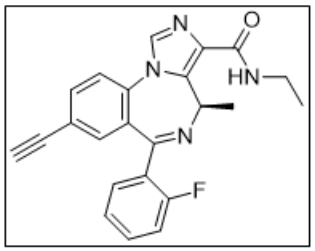
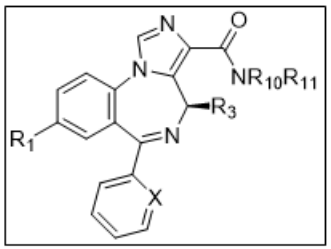
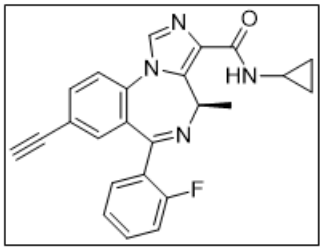
GL-II-73



Supplementary Figure 2. Estimate maximum free brain concentrations of 5 mg/kg of GL-I-54 and 5 mg/kg of GL-II-73

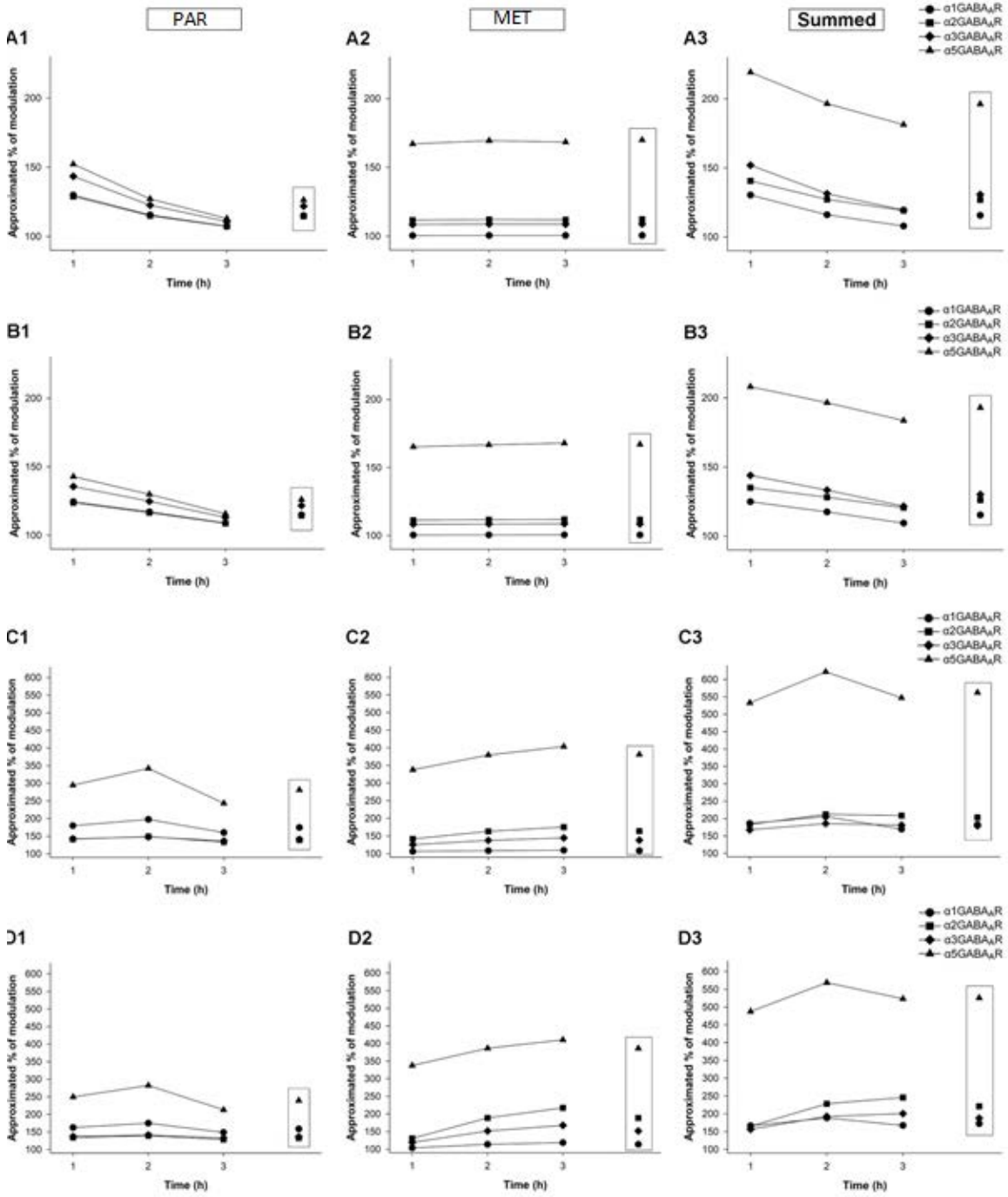
- **Supplementary Figure 2. Estimate maximum free brain concentrations of 5 mg/kg of GL-I-54 and 5 mg/kg of GL-II-73**
- Stepwise approach to estimate the maximum free brain concentrations of 5 mg/kg of GL-I-54 and 5 mg/kg of GL-II-73 (doses used in acute behavioral testing), and associate them with the range of corresponding $GABA_A$ receptor potentiation values (obtained in electrophysiological experiments). Maximum brain concentrations are achieved around 20 min after dosing (**Figure 1C** and Prevot et al.[9]). Blue content refers to GL-I-54 and green to GL-II-73. White and nuances of the grey and black color at the right bottom graph refer to the particular α subunit of $GABA_A$ receptors, as indicated in the upper right table. **Step 1** – brain concentrations (ng/g) determined 20 min after intraperitoneal dosing of 3 mg/kg GL-I-54 or GL-II-73 to male mice, respectively (n = 3 per compound); **Step 2** – estimation of maximum brain concentrations (ng/g) for 5 mg/kg of GL-I-54 and 5mg/kg of GL-II-73, obtained by multiplying Step 1 concentrations with the factor 5/3 (=1.67), based on an assumption that both GL-I-54 and GL-II-73 display a first-order pharmacokinetics (pharmacokinetics of GL-II-73 is not saturated at 3 and 10 mg/kg, since the increase in the concentration of the compound is proportionate); **Step 3** – free brain concentrations (ng/g) obtained by multiplying Step 2 concentrations with the free fractions in the brain determined by rapid equilibrium dialysis (0.1149 for GL-I-54 and 0.1214 for GL-II-73); **Step 4** – adjusting the Step 3 concentrations (ng/g) for the brain density (1.04 g/ml) and converting the units to ng/ml; **Step 5** – further conversion of units to nmol/l (unit used in electrophysiological experiments) by multiplying Step 4 concentrations with 1000/386.42 (386.42 g/mol is a molecular weight of GL-I-54 and GL-II-73) – the comparable estimated maximum free brain concentrations (nmol/l) of 5 mg/kg GL-I-54 and 5 mg/kg of GL-II-73 are now obtained; **Step 6** – association of Step 5 concentrations with the electrophysiological results – the estimated concentrations closely correspond to 100 nmol/l or, to a lesser extent, to 330 nmol/l of a compound administered in electrophysiological experiment. This implies that, in acute behavioral experiments with 5 mg/kg dose, GL-I-54 likely potentiates α_1, α_2, α_3 and α_5 $GABA_A$ receptors, however, α_1 potentiation is mild. 5 mg/kg of GL-II-73, on the other hand, is fairly silent on all $GABA_A$ receptors, with the potential to mildly activate α_2 and α_5 receptors; on α_1 and α_3 receptors, nevertheless, it behaves as a null modulator. Due to such properties, the racemic mixture of 5 mg/kg of GL-I-54 and 5 mg/kg of GL-II-73 might display advantageous pharmacological profile in vivo. By complete attenuation of activity at α1 $GABA_A$ receptors with GL-II-73, the potentiation of α2, α3 and α5 $GABA_A$ receptors by GL-I-54 might become predominant, exhibiting favorable behavioral effects. Ø – potentiation < 120% (null), + – potentiation < 200% (mild), ++ – potentiation < 250% (moderate), +++ – potentiation ≥ 250 % (strong). For exact values of potentiation at $GABA_A$ receptors containing distinct α subunits, please refer to **Figure 1.**

Ligands that selectively potentiate GABAA receptors containing the α5 subunit

Genus Structure	Compound Structure	Chemical Name	Code #	Formula	M.W. (g/mol)
		(R)-8-ethynyl-6-(2-fluorophenyl)-N,4-dimethyl-4H-benzo[f]imidazo[1,5-a][1,4]diazepine-3-carboxamide	MP-III-022	C22H17FN4O	372,39
		(R)-8-ethynyl-6-(2-fluorophenyl)-N,N,4-trimethyl-4H-benzo[f]imidazo[1,5-a][1,4]diazepine-3-carboxam	GL-II-73	C23H19FN4O	386,42
		(R)-N-ethyl-8-ethynyl-6-(2-fluorophenyl)-4-methyl-4H-benzo[f]imidazo[1,5-a][1,4]diazepine-3-carboxamide	GL-II-74	C23H19FN4O	386,42
		(R)-N-cyclopropyl-8-ethynyl-6-(2-fluorophenyl)-4-methyl-4H-benzo[f]imidazo[1,5-a][1,4]diazepine-3-carboxamide	GL-II-75	C24H19FN4O	398,43

Example of a mouse neuropharmacokinetic study at two doses and in both sexes, with measurement of the parent molecule and its active metabolite in parallel

Dose (mg/kg)	Sex	Compound	Plasma parameters		Brain parameters		
			Unbound C_{max} (ng/mL)	Unbound AUC_{last} (ng•h/mL)	Unbound C_{max} (ng/g)	Unbound AUC_{last} (ng•h/g)	$K_{p,uu,brain}$
10	Male	PAR	596.91 ± 59.57	1190.81 ± 182.99	101.43 ± 14.43	135.57 ± 17.57	**0.11 ± 0.01**
		MET	5.74 ± 0.37	18.95 ± 3.04	11.00 ± 7.85	17.65 ± 8.21	**0.94 ± 0.44**
	Female	PAR	583.21 ± 118.68	1250.29 ± 35.89	75.71 ± 14.85	146.24 ± 17.64	**0.12 ± 0.01**
		MET	5.98 ± 0.22	27.42 ± 6.73	9.58 ± 2.97	22.68 ± 2.40	**0.86 ± 0.19**
60	Male	PAR	4460.62 ± 647.34	14155.58 ± 1779.64	753.08 ± 114.34	2394.52 ± 309.53	**0.17 ± 0.01**
		MET	19.23 ± 2.11	128.83 ± 20.62	92.97 ± 12.77	780.78 ± 80.14	**6.14 ± 0.81**
	Female	PAR	3353.97 ± 491.77	12205.66 ± 1200.87	545.73 ± 65.14	1821.04 ± 181.73	**0.15 ± 0.01**
		MET	23.58 ± 4.13	149.68 ± 19.49	93.64 ± 15.03	709.97 ± 85.62	**4.77 ± 0.59**


PAR
MET
Summed
α1GABAAR
α2GABAAR
α3GABAAR
α5GABAAR
A1
A2
A3
B1
B2
B3
C1
C2
C3
D1
D2
D3
Approximated % of modulation
Time (h)

In closing…

- There are distinct methodological hurdles that govern selection of techniques to be used (e.g. many substances may stick to the membrane of the microdialysis probe)
- Neuropharmacokinetic assessment of biologicals is especially challenging (the premise on the lack of brain exposure to such pharmaceuticals is misleading)
- The establishment of clear guidelines for the assessment of $K_{p,uu,brain}$ by regulatory authorities is still pending
- The critical moment in translational approach is to select a pharmacological marker that reflects the desired therapeutic effect as accurately as possible
- Wider use of translational brain imaging technologies (such as PET) in CNS drug development programs would increase the translational validity of neuropharmacokinetic studies (but: general lack of tracers that would be highly selective for subpopulations of receptors in vivo, such are each of the four populations of GABAA receptors)

Artificial intelligence and the human race: Is it easier to create a shared brain than to use one's own?

Vesna Knežević, journalist

In reality, artificial intelligence possesses the consciousness of a graphite pencil

Sepp Hochreiter, a pioneer in the field of Artificial Intelligence

How about neuropharmacokinetics?

The New England Journal of Medicine Volume 339 Number 12 · 841

840 · September 17, 1998

Alternative Medicine — The Risks of Untested and Unregulated Remedies

It is time for the scientific community to stop giving alternative medicine a free ride. There cannot be two kinds of medicine — conventional and alternative. There is only medicine that has been adequately tested and medicine that has not, medicine that works and medicine that may or may not work. Once a treatment has been tested rigorously, it no longer matters whether it was considered alternative at the outset. If it is found to be reasonably safe and effective, it will be accepted. But assertions, speculation, and testimonials do not substitute for evidence. Alternative treatments should be subjected to scientific testing no less rigorous than that required for conventional treatments.

Marcia Angell, M.D.
Jerome P. Kassirer, M.D.

Thanks for joint work, consultations and discussions to researchers and colleaugues from University of Belgrade – Faculty of Pharmacy:

Prof. Dr. Bojan Marković, Department of Pharmaceutical Chemistry

Dr. Anja Santrač, Department of Pharmacology (previous)

Dr. Branka Divović Matović, Department of Pharmacology

Dr Tamara Timić Stamenić, Department of Pharmacology (previous)

Dr Aleksandar Obradović, Department of Physiology (previous)

Dr Bojan Batinić, Department of Physiology (previous)

Dr Marija Milić (nee Milinković), Department of Pharmacology (previous)

Dr Srđan Joksimović, Department of Pharmacology (previous)

Dr. Tanja Ilić (nee Isailović), Department of Pharmaceutical Technology and Cosmetology

Dr Sanela Savić (nee Đorđević), Department of Pharmaceutical Technology and Cosmetology (previous)

Assist. PharmM Aleksandra Vidojević, Department of Pharmacology

Assist. PharmM Tamara Stanković (nee Radulović), Department of Pharmacology (previous)

Assist. PharmM Jelena Mitrović, Department of Pharmaceutical Technology and Cosmetology

Assist. PharmM Jelena Đoković, Department of Pharmaceutical Technology and Cosmetology

Assoc. Prof. Dr. Vladimir Dobričić, Department of Pharmaceutical Chemistry

Prof. Dr. Katarina Vučićević, Department of Pharmacokinetics and Clinical Pharmacy

Prof. Dr. Snežana Savić, Department of Pharmaceutical Technology and Cosmetology

…and also collaboratory teams

James M Cook group in Milwaukee

Margot Ernst group in Vienna (previously lead by Werner Sieghart)