Esquizofrenia

Avanços nos Tratamentos Biológicos

Paulo Belmonte de Abreu

XVI JORNADA CELPCYRO & VII SIMPÓSIO CCYM SOBRE SAÚDE MENTAL

RESOLUÇÃO CFM nº 1.595/2.00O Conselho Federal de Medicina

- No uso das atribuições conferidas pela Lei nº 3.268, de 30 de setembro de 1957, regulamentada pelo Decreto nº 44.045, de 19 de julho de 1958,

- RESOLVE:
- Art. 2º - Determinar que os médicos, ao proferir palestras ou escrever artigos divulgando ou promovendo produtos farmacêuticos ou equipamentos para uso na medicina, declarem os **agentes financeiros que patrocinam suas pesquisas e/ou apresentações, cabendo-lhes ainda indicar a metodologia empregada em suas pesquisas – quando for o caso – ou referir a literatura e bibliografia que serviram de base à apresentação, quando essa tiver por natureza a transmissão de conhecimento proveniente de fontes alheias.**

- Brasília-DF, 18 de maio de 2.000.
- EDSON DE OLIVEIRA ANDRADE — RUBENS DOS SANTOS SILVA
- Presidente — Secretário-Geral

R1595CFM

- Agentes financeiros que patrocinam
  - Pesquisas: CNPq, CAPES, FIPE HCPA
  - Apresentação: Nenhum
- Metodologia empregada:
  - Pubmed meta-analises e ECR 2 anos
  - Evidências M-A:
  - Experiência HCPA

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schizophrenia treatment advances

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RESULTS BY YEAR

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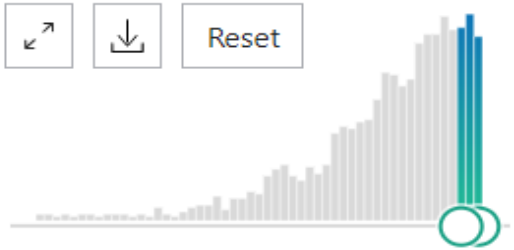

2020-2022

167 results Page 1 of 17

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Cite

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Peripheral biomarkers of **treatment**-resistant **schizophrenia**: Genetic, inflammation and stress perspectives.

Jiao S, Cao T, Cai H.

Front Pharmacol. 2022 Oct 12;13:1005702. doi: 10.3389/fphar.2022.1005702. eCollection 2022.

PMID: 36313375 Free PMC article. Review.

Treatment-resistant **schizophrenia** (TRS) often results in severe disability and functional impairment. ...Although mounting studies have identified certain clinical factors and neuroimaging characteristics

CENTRO DE ESTUDOS DE LITERATURA E PSICANÁLISE CYRO MARTINS

CYM ASSOCIAÇÃO DE PSIQUIATRIA CYRO MARTINS

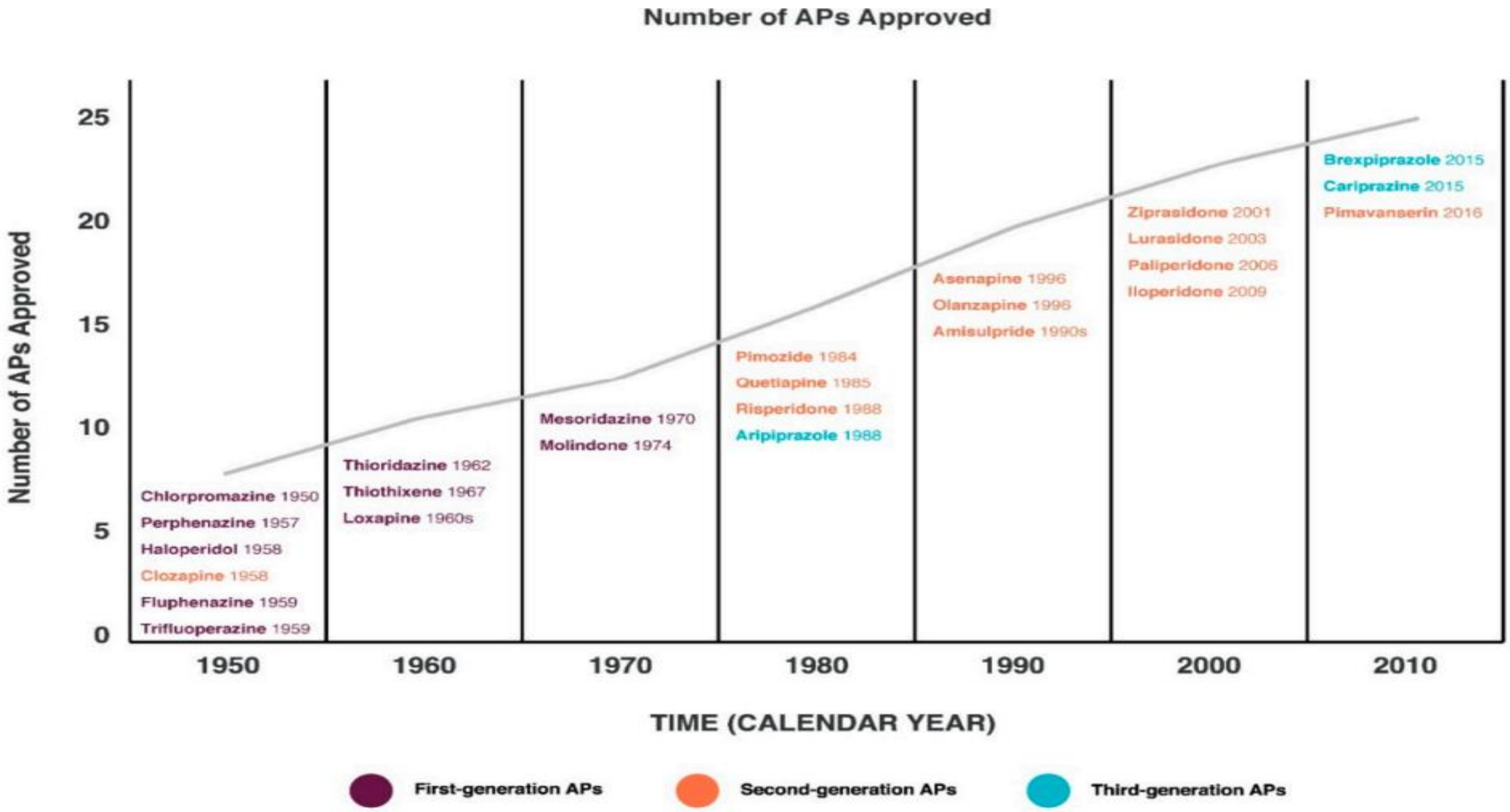


Figure 1. Timeline of antipsychotics (APs) approved by the Food and Drug Administration (FDA) [19].

Avanços em Esquizofrenia

- Medicamentos:
  - Dopaminérgicos
  - Muscarínicos
  - GABA
  - Antiinflamatórios
  - Imunomoduladores
- Intervenções – Estimulação Cerebral
  - tDCS
  - TMS/EMT
  - CART

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 July 19; 11(7): 277-296

DOI: 10.5498/wjp.v11.i7.277

ISSN 2220-3206 (online)

REVIEW

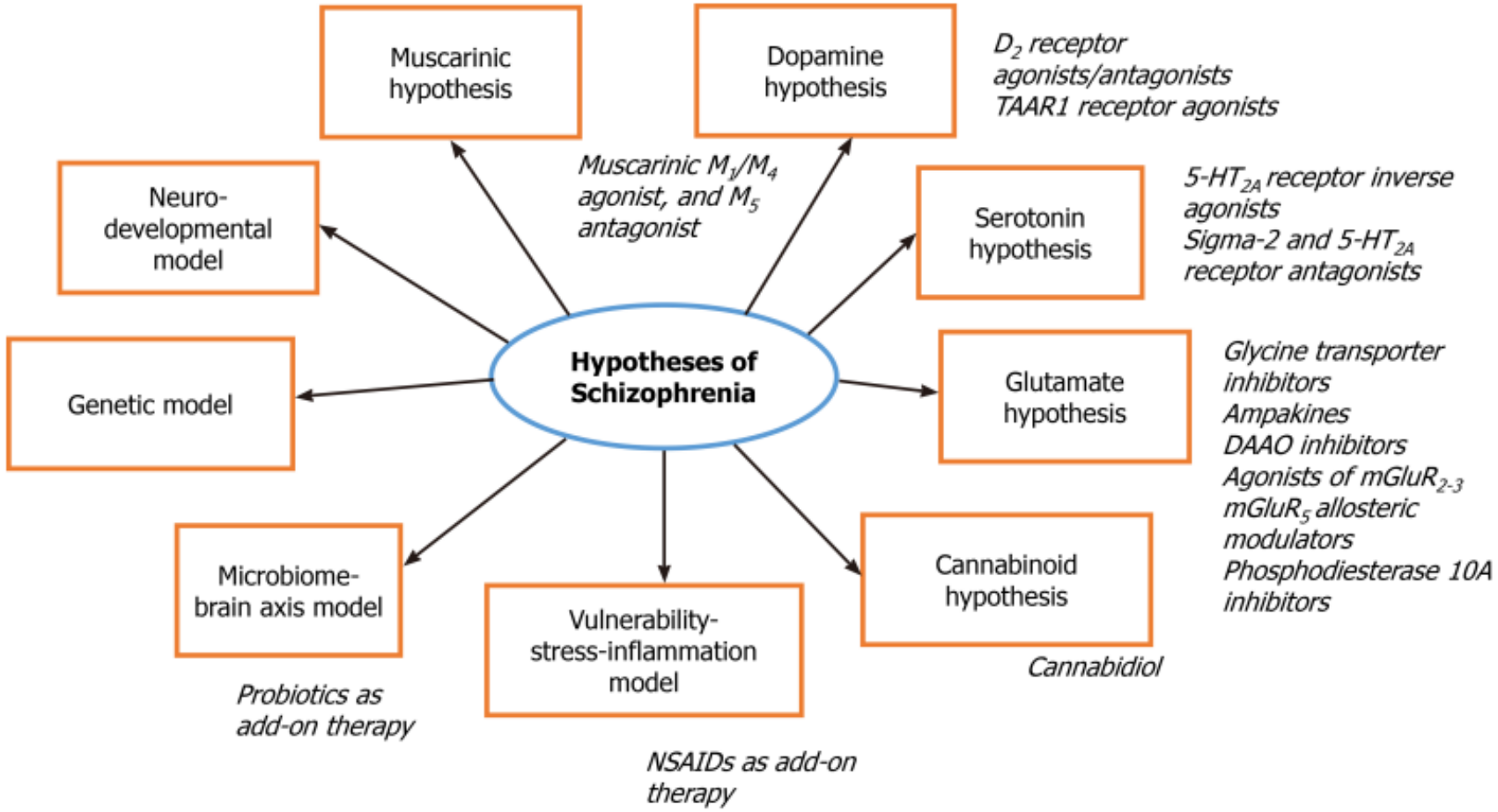
Novel approaches in schizophrenia-from risk factors and hypotheses to novel drug targets

Matej Ľupták, Danica Michaličková, Zdeněk Fišar, Eva Kitzlerová, Jana Hroudová

Table 1 Possible diagnostic/theranostic immunologic biomarkers in schizophrenia

Parameter	Serum/plasma/peripheral blood	CSF
Pro-inflammatory cytokines	↑ IL-6, IFN-γ, IL-1RA, IL-1β, IL-6, IL-8, IL-12, sIL-2R, TGF-β, and TNF-α	↑ IL-1β, IL-6 and IL-8
Anti-inflammatory cytokines	↓ IL-10 and IL-4	
Acute phase proteins	↑ CRP, haptoglobin, α-1 antitrypsin, and α-2 macroglobulin	
Antibodies	↑ Anti-cardiolipin IgG and anti-NMDA receptor titers	
Immune cells	↑ CD4+, CD3+ and CD56+	
Other biomolecules/metabolites	↓ Creatine kinase m/B, MMP3, ACE, cortisol, TBG, α-2 macroblobulin, thrombopoietin, TSH, and ICAM-1, P-selectin	

Ľupták M *et al*. Novel approaches in schizophrenia



Avanços no tratamento medicamentoso

- Monitoração por nível sérico
- Novas apresentações:
  - IM LA/AP: 1 mês, 3 meses, 6 meses
  - SL sublingual
  - Oral LA
- Novos agentes dopaminérgicos
- Agentes não-dopaminérgicos

Monitoração por Nível sérico de antipsicóticos

Psychopharmacology (2022) 239:3377–3391
https://doi.org/10.1007/s00213-022-06233-2

REVIEW

Therapeutic Reference Range for Aripiprazole in Schizophrenia Revised: a Systematic Review and Metaanalysis

Xenia M. Hart[1,13] · Christoph Hiemke[2,13] · Luzie Eichentopf[1] · Xenija M. Lense[1] · Hans Willi Clement[3,13] · Andreas Conca[4,13] · Frank Faltraco[5,13] · Vincenzo Florio[4] · Jessica Grüner[3] · Ursula Havemann-Reinecke[6,13] · Espen Molden[7] · Michael Paulzen[8,13] · Georgios Schoretsanitis[9,10,11,13] · Thomas G. Riemer[12] · Gerhard Gründer[1,13]

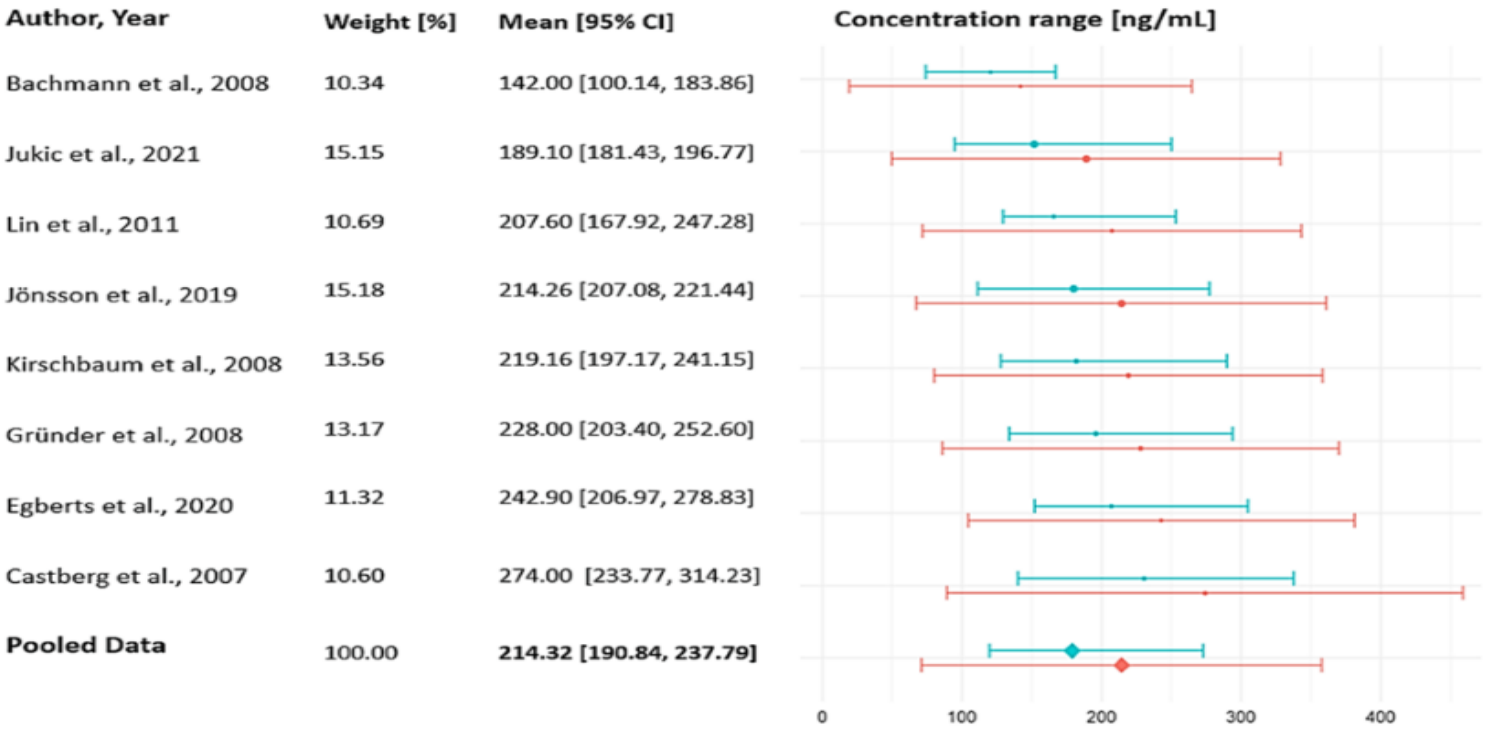


Fig. 4 Target ranges for ARI [ng/ml] (N= 3,778, Combined range mean ± SD: 71–358, combined interquartile range: 120–273, mean concentration 214 [191, 238] ($Q = 52.12$, $df = 7$, $p < .0001$, $I^2 = 93.2$, $T^2 = 932.1$))(Mean ± SD ranges of studies depicted as red lines, 25^{th}–75^{th} interquartile ranges of studies depicted as blue lines.)

Psychopharmacology (2022) 239:3377–3391
https://doi.org/10.1007/s00213-022-06233-2

REVIEW

Check for updates

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- Uso de monitoração no sangue: Clozapina e Aripiprazol
- Faixa de referência terapêutica para Aripiprazol
  - AI: 120 - 273 ng/ml:
    - 120 ng/ml: 9 mg 1 X dia.
    - 270 ng/ml: 20 mg 1 X dia
  - LA, AM e AL: 300 mg e 463 mg /intervalo proposto.

Novas apresentações

Longa-Longa Ação
Agentes sublinguais
Filme

Neuropsychiatric Disease and Treatment

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Comparing Relapse Rates in Real-World Patients with Schizophrenia Who Were Adequately versus Not Adequately Treated with Paliperidone Palmitate Once-Monthly Injections Before Transitioning to Once-Every-3-Months Injections

Ibrahim Turkoz[1], Mehmet Daskiran[1], H Lynn Starr[2], Dean Najarian[2], Oliver Lopena[2], Camilo Obando[2], Alexander Keenan[3], Carmela Benson[3], Srihari Gopal[4]

análise do mundo real: tratamento adequado com PP1M antes da transição para PP3M associado a taxas de recaída mais baixas e maior tempo antes de recaída em esquizofrenia. tratamento inicial adequado com PP1M dá melhor resultado no tratamento subsequente com PP3M.

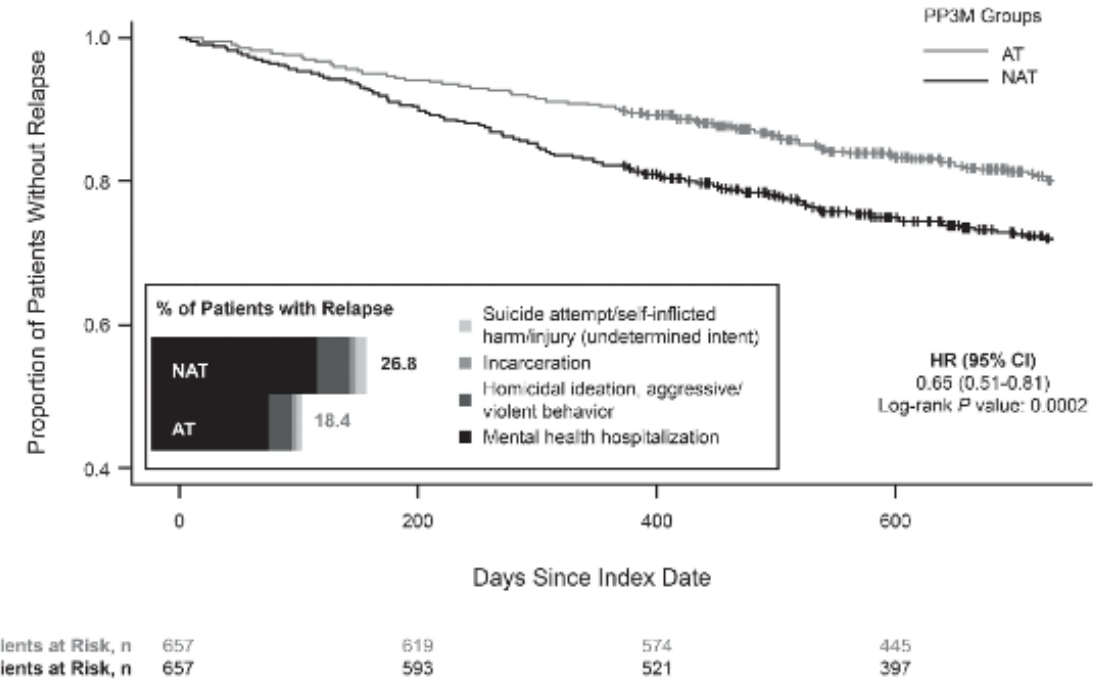
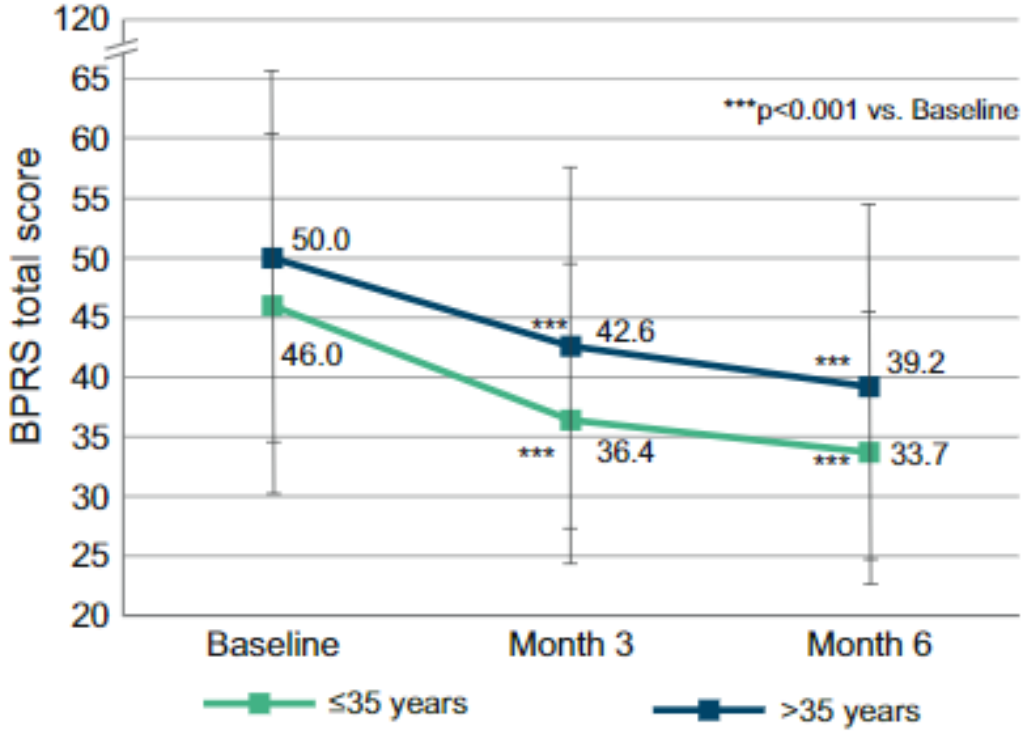
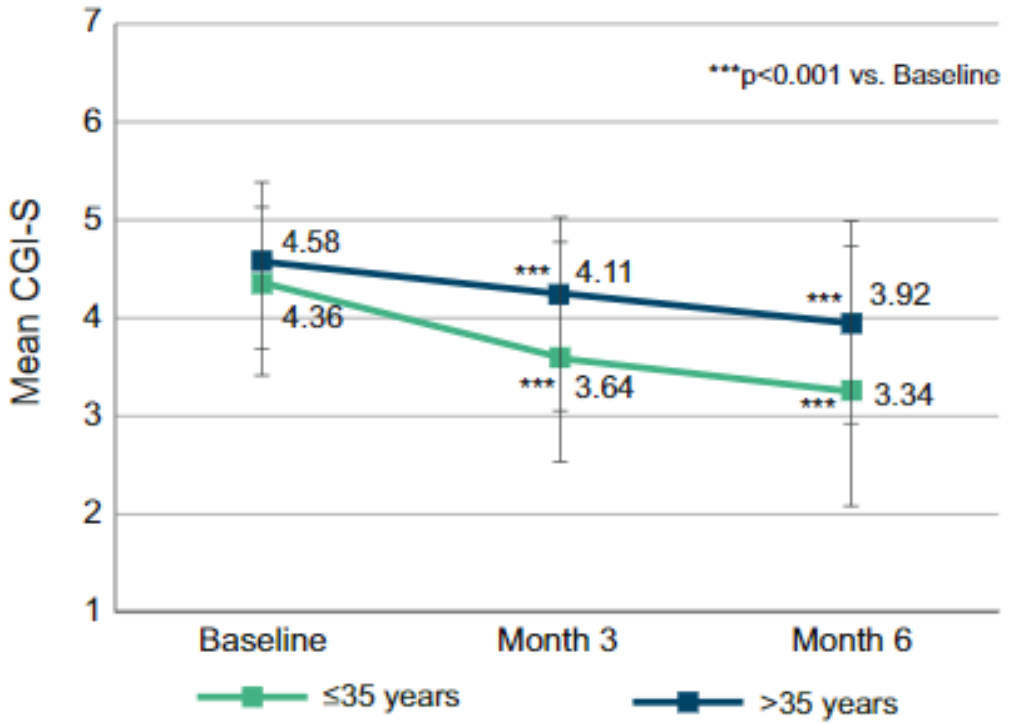


Figure 2 Time to first relapse and reasons for relapse[a] among eligible IBM MDCD patients.
Note: [a]One patient in the AT cohort had a relapse described as "incarceration; homicidal ideation"; this patient is included in both the "homicidal ideation, aggressive/violent behavior" and "incarceration" bars.
Abbreviations: AT, adequately treated; CI, confidence interval; HR, hazard ratio; NAT, not adequately treated; PP3M, paliperidone palmitate once-every-3-months.

Schöttle D, Clerzius G,Janetzky W, Oluboka O, Roy M-A, Therrien F,Wiedemann K (2022). Real-world effectivenessof aripiprazole once-monthly REACT study:Pooled analysis of two noninterventional studies. European Psychiatry,65(1),





Novas formulações

Patch transdérmico

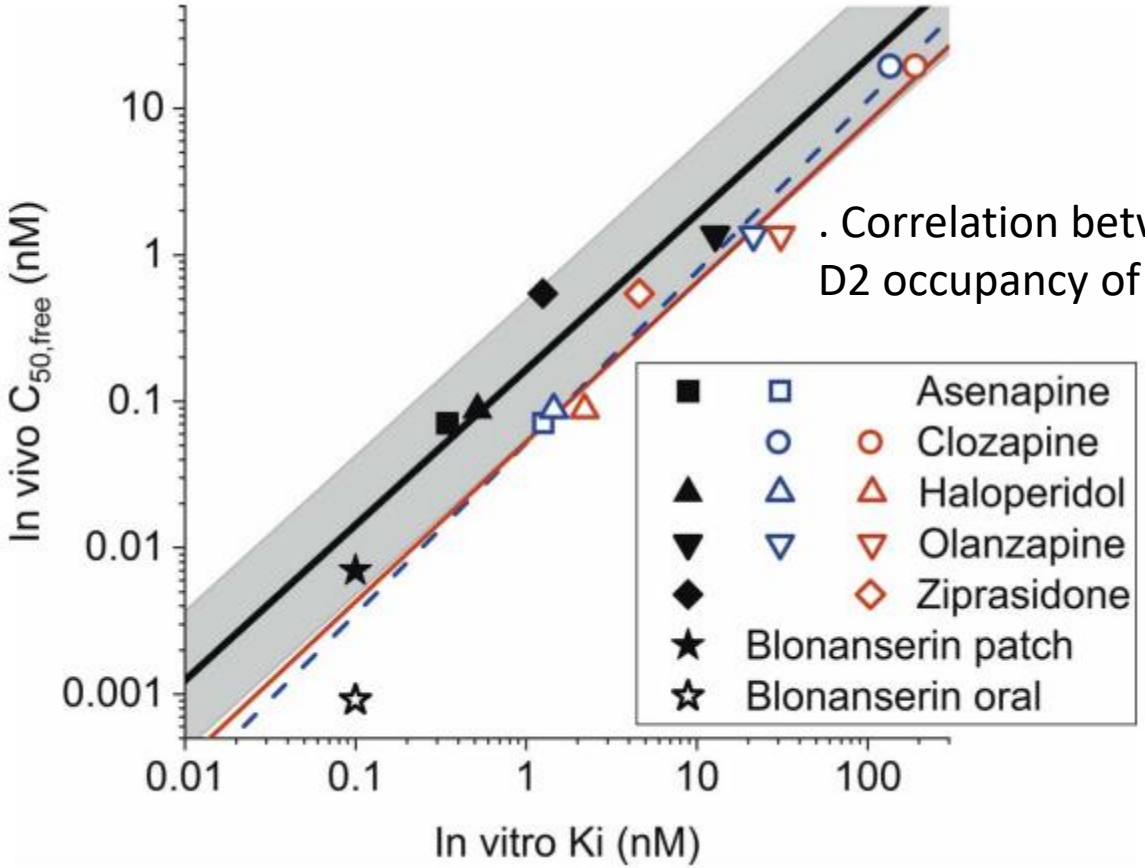
Blonanserina

Prediction of Corresponding Dose of Transdermal Blonanserin to Oral Dose Based on Dopamine D_2 Receptor Occupancy

Unique Characteristics of Blonanserin Transdermal Patch

Yoshiko Tomita, PhD,[1] Takeshi Takagaki, MS,[1] Atsushi Kitamura, MS,[1] Erika Wada, MS,[2] Hironori Nishibe, MS,[3] Amane Tateno, MD, PhD,[4] and Yoshiro Okubo, MD, PhD[4]

- Blonanserin (Lonasen; Sumitomo) Japão VO e transdérmico; alta afinidade D2R, D3R e 5-HT2AR
- Baixa afinidade **D1,4.2,5R, 5-HT1A,2B,2C,3-7R**, M1R e α1,2-/β-AdrR



. Correlation between in vitro Ki and in vivo C50,free values for D2 occupancy of various drugs for schizophrenia.

Leslie Citrome, et ali Sublingual Dexmedetomidine for the Treatment of Acute Agitation in AdultsWith Schizophrenia or Schizoaffective Disorder:A Randomized Placebo-Controlled Trial J Clin Psychiatry 83:6, November/December 2022

Dexmedetomidina filme sublingual (IGALMI, BioXcel Therapeutics, Inc., New Haven, CT)

Aprovado pelo FDA em 5 de abril de 2022 (1999: EV sedação pacientes intubados/ ventilados mecanicamente UTI/ sedação não intubados procedimentos cirúrgicos)

Tratamento agudo agitação adultos associada à esquizofrenia ou transtorno bipolar I ou II.

Agonista Receptor α2-adrenérgico

Reformulação da dexmedetomidina filme sublingual: uso mais amplo em ambientes psiquiátricos

Controle de Agitação sem uso de medicação intramuscular de antipsicóticose/BZD

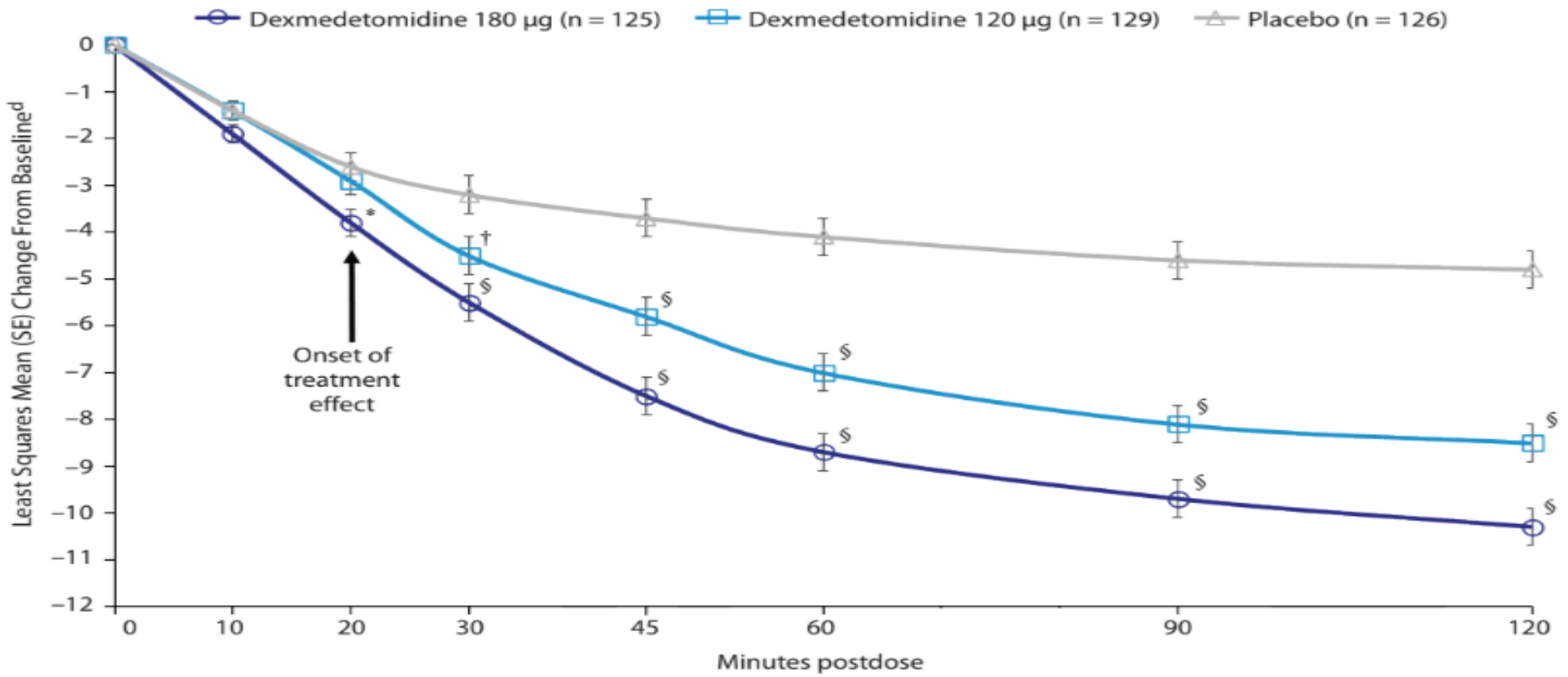
Formulação não invasiva: cooperação dos pacientes/potencial de melhorar a experiência geral do paciente/cooperação futura entre os pacientes e prestadores de cuidados.

Filme sublingual absorvido evita metabolismo hepático de primeira passagem

Maior biodisponibilidade de dexmedetomidina do que formulações ingeridas

Dexmetomedina

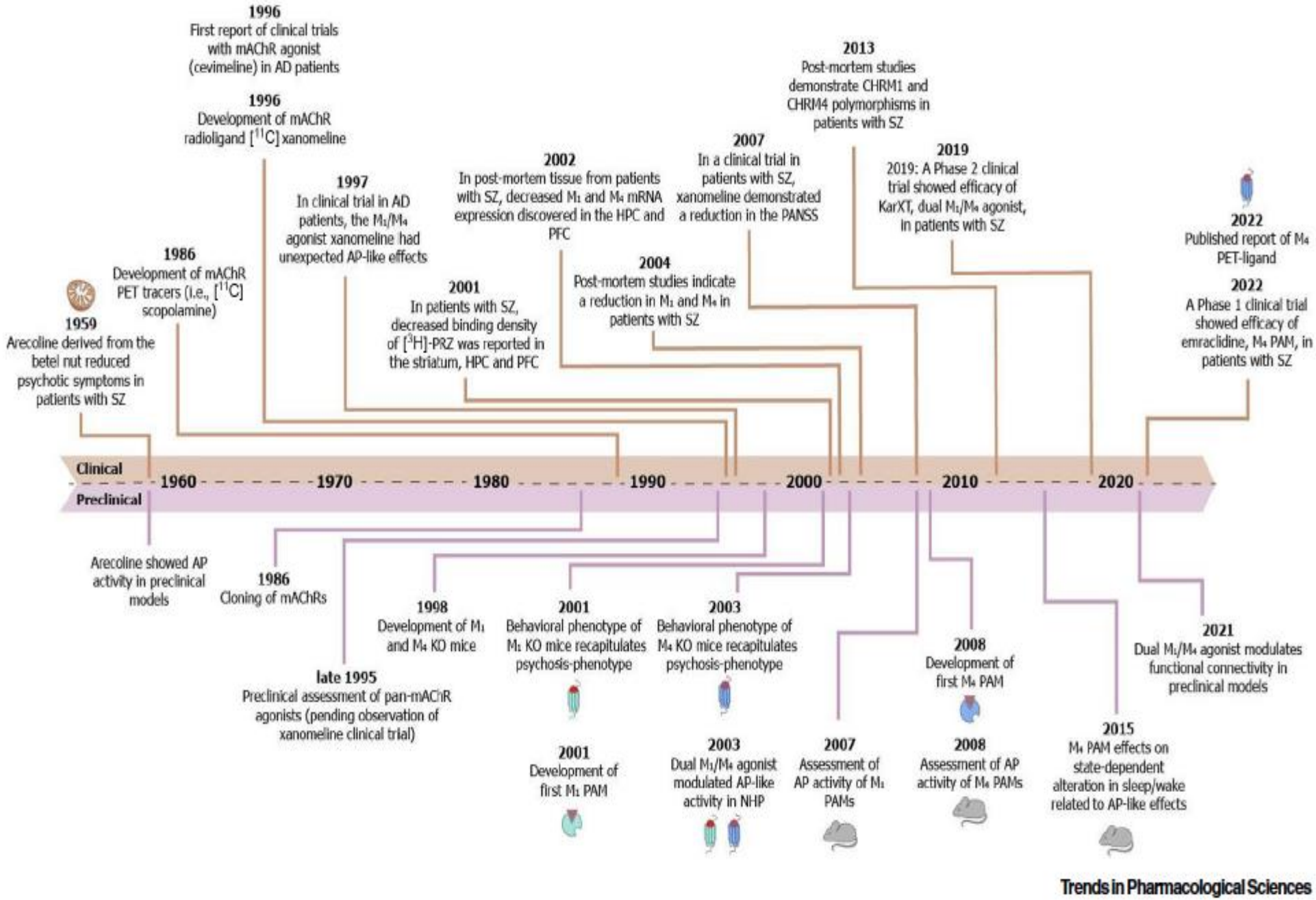
Figure 2. Primary and Secondary Efficacy Endpoints: Least Squares Mean (SE) Change From Baseline in the PEC Total Score[a]

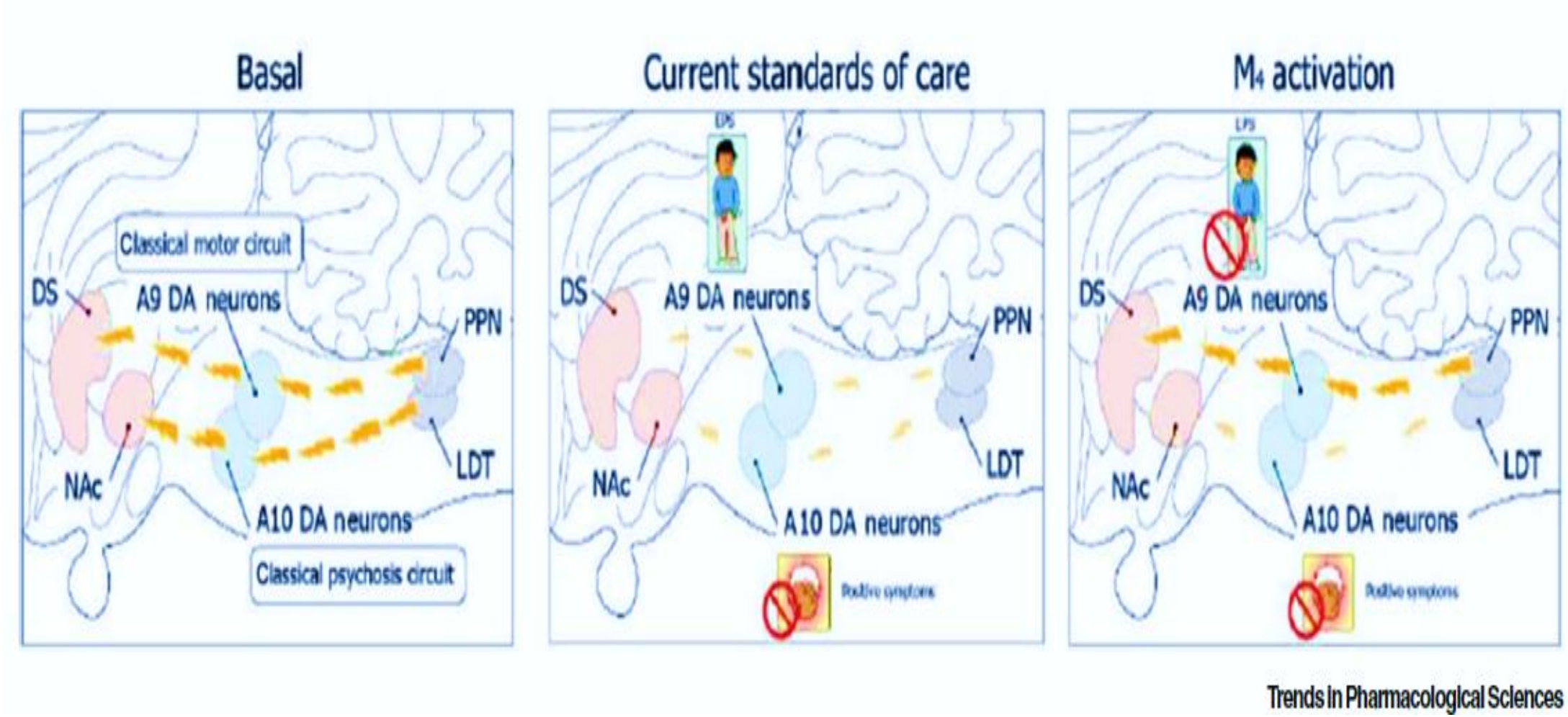


[a]*P* values were calculated from a restricted maximum likelihood repeated measures mixed model on change from baseline values. Covariates were baseline PEC score (composed of 5 items with a range of 5 [absence of agitation] to 35 [extremely severe]), age stratum, study site, timepoint (including all 7 timepoints from 10 minutes to 2 hours postdose), treatment group, baseline PEC score–by-timepoint interaction term, and treatment group–by-timepoint interaction term.
*$P = .003$ vs placebo.
†$P = .008$ vs placebo.
§$P < .001$ vs placebo.
Abbreviations: PEC = Positive and Negative Syndrome Scale-Excited Component, SE = standard error.

Agentes sobre sistemas além de DA

- Agentes sobre Acetilcolina
- Receptores Muscarínicos
- Receptor TAAR1


1959
Arecoline derived from the betel nut reduced psychotic symptoms in patients with SZ
1986
Development of mAChR PET tracers (i.e., [11C] scopolamine)
1996
First report of clinical trials with mAChR agonist (cevimeline) in AD patients
1996
Development of mAChR radioligand [11C] xanomeline
1997
In clinical trial in AD patients, the M1/M4 agonist xanomeline had unexpected AP-like effects
2001
In patients with SZ, decreased binding density of [3H]-PRZ was reported in the striatum, HPC and PFC
2002
In post-mortem tissue from patients with SZ, decreased M1 and M4 mRNA expression discovered in the HPC and PFC
2004
Post-mortem studies indicate a reduction in M1 and M4 in patients with SZ
2007
In a clinical trial in patients with SZ, xanomeline demonstrated a reduction in the PANSS
2013
Post-mortem studies demonstrate CHRM1 and CHRM4 polymorphisms in patients with SZ
2019
2019: A Phase 2 clinical trial showed efficacy of KarXT, dual M1/M4 agonist, in patients with SZ
2022
Published report of M4 PET-ligand
2022
A Phase 1 clinical trial showed efficacy of emraclidine, M4 PAM, in patients with SZ
Clinical
Preclinical
1960
1970
1980
1990
2000
2010
2020
Arecoline showed AP activity in preclinical models
1986
Cloning of mAChRs
late 1995
Preclinical assessment of pan-mAChR agonists (pending observation of xanomeline clinical trial)
1998
Development of M1 and M4 KO mice
2001
Behavioral phenotype of M1 KO mice recapitulates psychosis-phenotype
2001
Development of first M1 PAM
2003
Behavioral phenotype of M4 KO mice recapitulates psychosis-phenotype
2003
Dual M1/M4 agonist modulated AP-like activity in NHP
2007
Assessment of AP activity of M1 PAMs
2008
Development of first M4 PAM
2008
Assessment of AP activity of M4 PAMs
2015
M4 PAM effects on state-dependent alteration in sleep/wake related to AP-like effects
2021
Dual M1/M4 agonist modulates functional connectivity in preclinical models
Trends in Pharmacological Sciences



Ativação dupla R Mu de acetilcolina M1/M4 (mAChR) estimulo seletivo N DA A10 (VTA), 'circuito clássico da psicose sem ativar A9 DA (SN, 'circuito motor clássico'. '. centros DA do mesencéfalo (azul) controlados via centros colinérgicos do rombencéfalo (cinza) (núcleo tegmental látero-dorsal (LDT) e núcleo pedunculopontino (PPN)) AP atuais atividade D2R (-) ambas as vias DA: desligam circuito motor + circuito de psicose. Ativador M4R desliga seletivamente N A10 DA sem afetar via motora (N A9)

Clinical development						
Drug	Mechanism of action	Company	Disorder(s)	Clinical development phase	Completed clinical trial	Ongoing clinical trial(s)
KarXT	Xanomeline (dual M_1/M_4 receptor-preferring agonist) and trospium (peripherally restricted mAChR antagonist) combination	Karuna Therapeutics	Schizophrenia, Alzheimer's disease	Phase 3	NCT03697252	NCT04820309
						NCT04659174
						NCT05304767
					NCT04659161	NCT05145413
						NCT04738123
						NCT03244228
HTL0016878	Selective M_4 receptor agonist	Neurocrine Biosciences	Schizophrenia, Alzheimer's disease	Phase 2		NCT05227703
Emraclidine (CVL-231)	Selective M_4 receptor positive allosteric modulator	Cerevel Therapeutics	Schizophrenia	Phase 2	NCT04136873	NCT05245539
						NCT05227690
ML-007[i]	Dual M_1/M_4 receptor-preferring agonist	Maplight Therapeutics	Schizophrenia, dyskinesia	Phase 1		

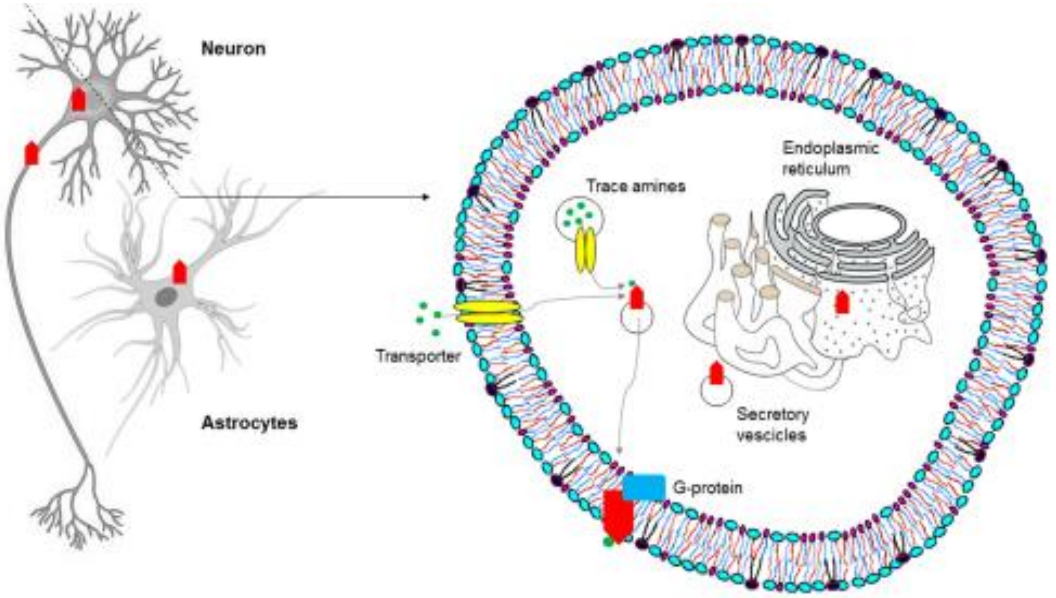
Preclinical pipeline programs			
Program	Compound	Disorder(s)	Company
M_4 receptor orthosteric agonist	Not disclosed	Schizophrenia	Sosei Heptares
	Not disclosed	Not disclosed	Sumitomo Dainippon Pharma
Dual M_1 and M_4 receptor orthosteric agonist	Not disclosed	Schizophrenia, Alzheimer's disease psychosis	Neurocrine Biosciences
M_4 receptor positive allosteric modulator	Not disclosed	Schizophrenia, other neuropsychiatric disorders	Addex Therapeutics

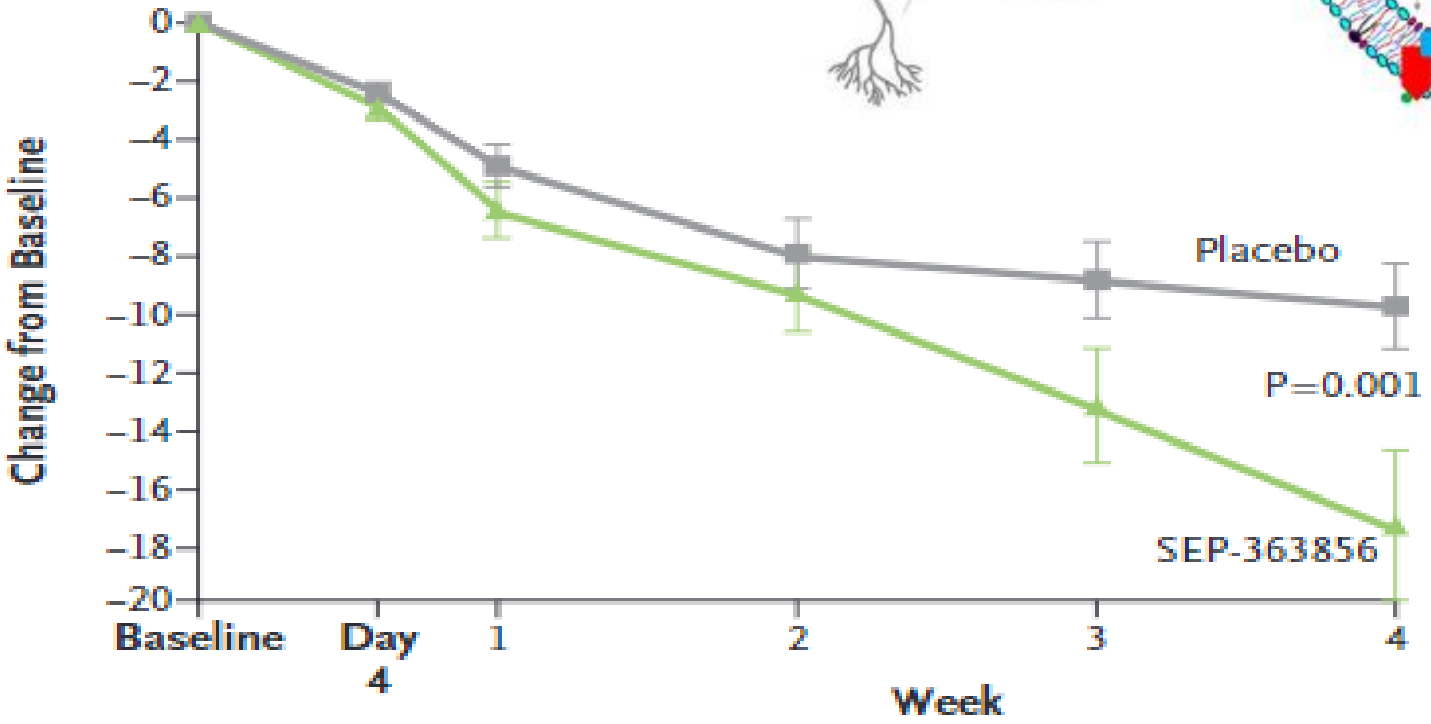
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 16, 2020 VOL. 382 NO. 16

A Non–D2-Receptor-Binding Drug for the Treatment of Schizophrenia

Kenneth S. Koblan, Ph.D., Justine Kent, M.D., Seth C. Hopkins, Ph.D., John H. Krystal, M.D., Hailong Cheng, Ph.D., Robert Goldman, Ph.D., and Antony Loebel, M.D.





No. of Patients						
Placebo	125	125	122	117	113	100
SEP-363856	120	120	115	109	102	96

- Agentes Glutamatérgicos

Pharmacology, Biochemistry and Behavior 219 (2022) 173446

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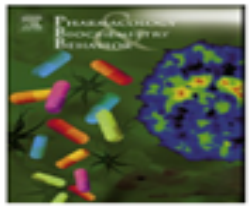
journal homepage: www.elsevier.com/locate/pharmbiochembeh

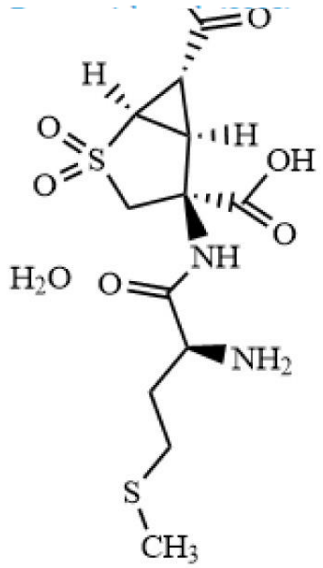


Clinical investigations of compounds targeting metabotropic glutamate receptors

Jeffrey M. Witkin [a,b,c,*], Kamal P. Pandey [b], Jodi L. Smith [a]

Table 6
Clinical studies that have been disclosed to the public on the effects of mGlu2 and mGlu2/3 receptor agonists or potentiators in chronological order of publication.

Compound	Receptors	Study	Findings	Reference
LY354740	Both	Panic disorder patients 100 and 200 mg	No separation from placebo. Paroxetine (60 mg) showed a trend.	Bergink and Westenberg (2005)
Pomaglumetad methionil (LY2140023 hydrate)	Both	Phase 2 Schizophrenia Double blind Olanzapine and placebo	Decreases in positive and negative symptoms as with olanzapine at 4 weeks.	Patil et al. (2007)
LY544344	Both	Phase 2 GAD Double blind Two doses b.i.d. and placebo	Improvements in HA and CGI. Response and remission > placebo. Well tolerated.	
Pomaglumetad methionil	Both	Phase 2 schizophrenia Double blind 5–40 mg, b.i.d. vs olanzapine and placebo	Neither drug separated from placebo at 8 weeks on PANNS total scores. High placebo effect. Seizures reported in pomaglumetad group.	
Pomaglumetad methionil	Both	Phase 2 schizophrenia with predominant negative symptoms Open label One dose b.i.d. vs SOC	Comparable improvement in PANNS scores at 6–8 weeks. SOC > Pomaglumetad at 24 weeks. Pomagluglumetad = SOC on negative symptoms. Differential adverse events.	
Pomaglumetad methionil	Both	Phase 2 schizophrenia 20 mg b.i.d. in conjunction with SOC (aripiprazole, olanzapine, risperidone, or quetiapine)	Drug combination did not significant separate from Pomaglumetad + SOC on NSA-16 or cognition at 16 weeks	
Pomaglumetad methionil	Both	Phase 3 schizophrenia Double blind 40 mg b.i.d. vs aripiprazole	Aripiprazole > Pomaglumetad at 24wk. Pomaglumated produced less weight gain.	
Pomaglumetad methionil	Both	Phase 1b schizophrenia Randomized, double-blind 40 or 80 mg, b.i.d. or placebo	Withdrawal from pomaglumetad did not produce withdrawal symptoms on the DSC-MR scale after 2 weeks of daily treatment.	
Pomaglumetad methionil	Both	Phase 2 schizophrenia Subpopulation which excluded non-Hispanic white patients with the A/A genotype at the HTR2A SNP rs7330461. 40 and 80 mg b.i.d. vs. risperidone	No overall significant effect on PANNS scores for pomaglumetad at either dose in either the general or subpopulation. Risperidone was effective at 6 weeks.	
Pomaglumetad methionil	Both	Phase 2 schizophrenia Retrospective data analysis 40 and 80 mg b.i.d. vs. risperidone	The specific patient population of those that were early-in-disease or previously treated with D2R antipsychotic drugs showed greater improvement compared to placebo when treated with pomaglumetad, at 40 mg, but not 80 mg. Risperidone effects were not dependent on subgroup.	Kinon et al. (2015)



Pomaglumetad methionil
(LY2140023 hydrate)

Agentes reguladores de Canais de Cálcio

Table 1
Common and rare variant associations of LTCC and other VGCC genes with psychiatric disorders.

Subunit type	Channel type[a]	Channel name[a]	Subunit name	Gene symbol	Common variants[b,c]	Rare variants[b,d]
Alpha1 (α1)	L-type	$Ca_V1.1$	α1S	*CACNA1S*	Scz, XD	Scz
		$Ca_V1.2$	α1C	*CACNA1C*	**BD**, Scz, ASD, XD	ASD, BD, Scz
		$Ca_V1.3$	α1D	*CACNA1D*	Scz, XD	ASD, BD
		$Ca_V1.4$	α1F	*CACNA1F*		
	P/Q-type	$Ca_V2.1$	α1A	*CACNA1A*		
	N-type	$Ca_V2.2$	α1B	*CACNA1B*	**BD**	BD, Scz
	R-type	$Ca_V2.3$	α1E	*CACNA1E*	MDD, XD	
	T-type	$Ca_V3.1$	α1G	*CACNA1G*		Scz
		$Ca_V3.2$	α1H	*CACNA1H*		ASD, Scz
		$Ca_V3.3$	α1I	*CACNA1I*	Scz, ASD	
Beta (β)			β1	*CACNB1*		
			β2	*CACNB2*	Scz, **BD**, XD	ASD
			β3	*CACNB3*		
			β4	*CACNB4*		Scz
Alpha2delta (α2δ)			α2δ1	*CACNA2D1*	MDD	Scz
			α2δ2	*CACNA2D2*	Scz, XD	Scz
			α2δ3	*CACNA2D3*		ASD
			α2δ4	*CACNA2D4*	XD	Scz

[a] Channel type and name are defined by the α1 subunit.
[b] ADHD: attention-deficity hyperactivity disorder; ASD: autistic spectrum disorder. BD: bipolar disorder. MDD: major depression. Scz: schizophrenia. XD: cross-disorder (scz/BD/MDD/ADHD/ASD).
[c] Common variant locus associations reported in one or more GWAS. Results in boldface are genome-wide significant in the latest Psychiatric Genomics Consortium analyses of schizophrenia (Trubetskoy et al., 2022) and bipolar disorder (Mullins et al., 2021).
[d] Boldface denotes significant findings in the SCHEMA whole exome study of schizophrenia (Singh et al., 2022).

Agentes sobre sistema CB

Schizophrenia Research 164 (2015) 155–163

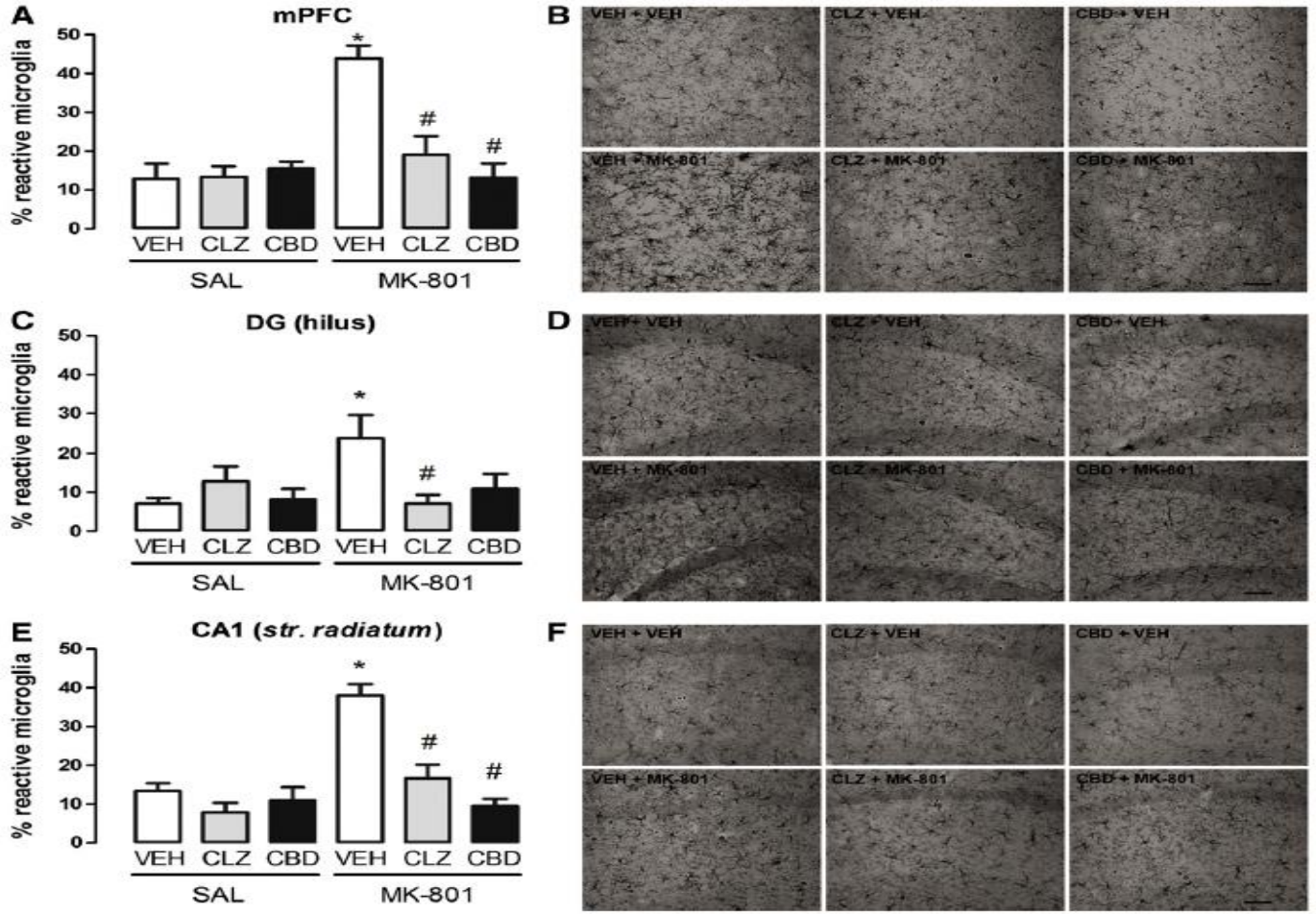
Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Decreased glial reactivity could be involved in the antipsychotic-like effect of cannabidiol

Felipe V. Gomes [a,b,*], Ricardo Llorente [c], Elaine A. Del Bel [b,d], Maria-Paz Viveros [e], Meritxell López-Gallardo [c], Francisco S. Guimarães [a,b,*]



Tratamento CBD ou clozapina atenua ou reverte alteração comportamental semelhante à esquizofrenia (modelo de antagonista do receptor NMDA MK-801): CBD efeitos semelhantes aos antipsicóticos
Propriedades anti-inflamatórias e neuroprotetoras do CBD: Inibição da ativação de microglia pode melhorar os sintomas da esquizofrenia.
Mecanismos destes efeitos precisam ser mais investigados.

molecules

MDPI

Review

The Nitric Oxide (NO) Donor Sodium Nitroprusside (SNP) and Its Potential for the Schizophrenia Therapy: Lights and Shadows

Elli Zoupa and Nikolaos Pitsikas *

- resultados emocionantes do primeiro conjunto de estudos [58,59] não reproduzidos subsequentemente. diferenças de protocolos:
  - efeitos antipsicóticos jovens, não fumantes, sintomas negativos graves e curso curto [58,59].
  - Sem perfil antipsicótico em pacientes mais velhos, fumantes, menos sintomas negativos e maior tempo de doença
- eficácia clínica de outros moduladores de NO em esquizofrenia: resultados contraditórios
- precursor de NO: L-arginina
- Doador NO gliceril trinitrato (GTN) primeiro episódio não melhorou sintomas
- Mononitrato de isossorbida doador de NO (ISMN) efeito sintomas positivos e funcionamento.

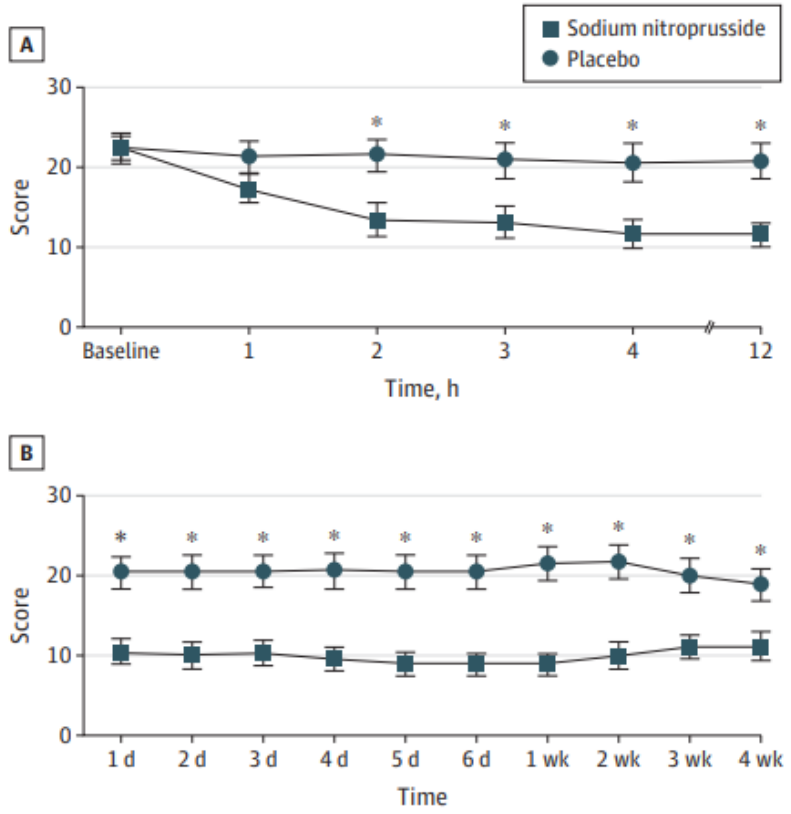
Original Investigation

Rapid Improvement of Acute Schizophrenia Symptoms After Intravenous Sodium Nitroprusside

A Randomized, Double-blind, Placebo-Controlled Trial

Jaime E. C. Hallak, MD, PhD; Joao Paulo Maia-de-Oliveira, MD; Joao Abrao, MD, PhD; Paulo R. Evora, MD, PhD; Antonio W. Zuardi, MD, PhD; Jose A. S. Crippa, MD, PhD; Paulo Belmonte-de-Abreu, MD; Glen B. Baker, PhD, DSc; Serdar M. Dursun, MD, PhD, FRCPC

Figure 2. Mean Total 18-Item Brief Psychiatric Rating Scale Scores



A, Scores during the first 12 hours; B, scores at 4 weeks. Asterisks indicate statistically significant *P* values as given in the text; error bars, SEMs.

Redirecionamento de medicamentos: SZ, BD e MDD

European Neuropsychopharmacology 61 (2022) 43-59

ELSEVIER

www.elsevier.com/locate/euroneuro

Charting the proteome landscape in major psychiatric disorders: From biomarkers to biological pathways towards drug discovery

Brisa S. Fernandes[a], Yulin Dai[a], Peilin Jia[a], Zhongming Zhao[a,b,c,d,*]

A: SZ, BD e MDD:

1. sistema imunoinflamatório:

anti TNF: infliximab e etanercept, inib HMG-COA redutase: macrolídeos, cefalosporinas e tetraciclinas.

2. inibidores da acetilcolinesterase.

3. inibidor da quinase dos receptores VEGF e EGFR (Vandetanibe)

4. inibidor do EGFR (gefitinibe)

B: SZ e MDD:

1. inibidor de C1 esterase (Conestat alfa)
2. curcumina, rosiglitazona e estradiol.

C: Exclusivamente SZ:

liraglutida, memantina, danazol e ácido micofenólico

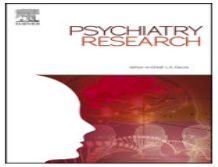
- Agentes Imunológicos em Esquizofrenia

Psychiatry Research 317 (2022) 114866

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres



From co-morbidity to transdiagnostic potential and novel immunotherapies for psychosis

Rachel Upthegrove

Commonly Studied Cytokines, Vascular Markers, and Related Measures of Inflammation in Psychosis			
Protein designation	Name	Category	Description and function[a]
CRP	C-reactive protein	General marker of inflammation	Acute-phase protein and peripheral marker of acute inflammation Produced in response to pro-inflammatory cytokines (IL-1 and IL-6) and lipopolysaccharides
FLT1	Vascular endothelial growth factor receptor–1	Vascular	Cell-surface receptor for vascular endothelial growth factors Involved in the development of embryonic vasculature, angiogenesis regulation, cell survival, cell migration, macrophage function, and chemotaxis
IFNγ	Interferon gamma	Pro-inflammatory cytokine	Produced by lymphocytes and is a potent activator of macrophages
IL-1β	Interleukin 1 beta	Pro-inflammatory cytokine	Induces prostaglandin synthesis, neutrophil influx and activation, T-cell activation and cytokine production, B-cell activation and antibody production, and fibroblast proliferation
IL-6	Interleukin 6	Pro-inflammatory cytokine	Activation leads to the regulation of the immune response, acute-phase reactions Plays an essential role in differentiating B cells
IL-8	Interleukin 8	Pro-inflammatory cytokine	Chemotactic factor that attracts neutrophils, basophils, and T cells involved in neutrophil activation It is released from several cell types in response to inflammatory stimuli
IL-10	Interleukin 10	Anti-inflammatory cytokine	Regulatory cytokine that has profound anti-inflammatory functions, limiting excessive tissue disruption caused by inflammation Limits macrophage and monocyte release of pro-inflammatory cytokines
IL-18	Interleukin 18	Pro-inflammatory cytokine	Pro-inflammatory cytokine that promotes the production of IFNγ from T and NK cells Enhances cytotoxic activity and proliferation of CD8+ T and NK cells and stimulates the production of IL13 and other cytokines
TNFα	Tumor necrosis factor alpha	Pro-inflammatory cytokine	Pro-inflammatory and apoptosis-inducing cytokine secreted by macrophages
TNFβ	Tumor necrosis factor beta	Pro-inflammatory cytokine	Pro-inflammatory and cytotoxic cytokine produced by lymphocytes
VEGFA	Vascular endothelial growth factor A	Vascular	Growth factor that induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis and induces permeabilization of blood vessels
VEGFD	Vascular endothelial growth factor D	Vascular	Growth factor active in angiogenesis, lymphangiogenesis and endothelial cell growth, stimulating their proliferation and migration and also has effects on the permeability of blood vessels

[a]Adapted from information accessed at https://www.uniprot.org/[216] and reproduced here under Creative Commons Attribution (CC BY 4.0) License, https://creativecommons.org/licenses/by/4.0/.

Risperidone combination therapy with adalimumab for treatment of chronic schizophrenia: a randomized, double-blind, placebo-controlled clinical trial Motamed, Mahsa[a] International Clinical Psychopharmacology: May 2022 - Volume 37 - Issue 3 - p 92-101 doi: 10.1097/YIC.0000000000000399

antifator de necrose tumoral alfa (TNF-α) adalimumabe esquizofrenia crônica.

ECR DC CP Hospital Roozbeh (Teerã, Irã)

adalimumabe + risperidona e

placebo + risperidona.

adalimumabe (40 mg) SC semanas 0 e 4.

PANSS semanas 0, 4 e 8 20 0 20 p

PANSS total ($t = 4,43$, $df = 38$, $P < 0,001$), negativo ($t = 2,88$, $df = 38$, $P = 0,006$) e psicopatologia geral ($t = 4,06$, $df = 38$, $P < 0,001$)

Efeito superior de adalimumab em comparação com o grupo placebo

PANSS + sem diferença significativa

Não houve diferença significativa entre os grupos em relação aos níveis de proteína C-reativa, interleucina (IL)-1β, TNF-α, IL-6 e IL-8 na linha de base e também na visita da semana 8 ($P > 0,05$ para todos).

terapia adjuvante adalimumabe eficaz sintomas de psicopatologia negativa e geral, sem efeitos colaterais.

Drug	Mechanism	Results	References
Non-steroidal anti-inflammatory drugs			
Celecoxib	Selective inhibition of COX-2.	Significant reduction in PANSS positive TRS symptom scores and overall PANSS score, but no significant change in negative TRS symptoms. Improvement in conceptual disorganization and abstract thinking by PANSS in patients with TRS.	[133,134]
Acetylsalicylic acid	Inhibition of COX-1 and c COX-2.	Improvement in PANSS symptoms.	[135,136]
Statins			
Simvastatin	Inhibition of HMG-CoA reductase, anti-inflammatory effect, reduction of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and CRP.	Decrease in negative symptom scores on the PANSS scale in patients with TRS, decrease in the total score on the PANSS scale.	[137]
Pravastatin	Inhibition of HMG-CoA reductase, anti-inflammatory effect, reduction of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and CRP.	Marked decrease in scores positive symptoms on the PANSS scale.	[138]
Corticosteroids			
Cortisone	Influence on carbohydrate and electrolyte metabolism, anti-inflammatory (inhibition of phospholipase A2), desensitizing and anti-allergic, immunosuppressive effects.	Most patients with Sch did not show significant changes in Sch symptoms.	[139]
Prednisolone	Suppression of the function of leukocytes and tissue macrophages. Limitation of migration of leukocytes to the area of inflammation, impairment of the ability of macrophages to phagocytosis, as well as to the formation of IL-1, inhibition of the activity of phospholipase A2, suppression of the release of COX-1 and COX-2, etc.	There was no significant difference in improvement in the severity of Sch symptoms with the placebo group in patients with Sch.	[140]

Drug	Mechanism	Results	References
	Monoclonal antibody		
Tocilizumab	Selective binding and suppression of expression and functional activity of IL-6 receptors.	No significant change in scores for positive and negative TRS symptoms, but improvement in BACS cognition.	[141,142]
	Cytokines		
- IFN-γ-1b	Activation of macrophages and induction of expression of the class II major histocompatibility complex molecule, inhibition of virus replication.	A pronounced decrease in the total PANSS score in patients with TRS.	[143]
	Intravenous immunoglobulins		
- IgG	Increasing the content of antibodies in the blood to a physiological level, creating passive immunity.	A pronounced decrease in the total PANSS score in patients with antibody positive psychosis. Most patients gave a clinical response to therapy.	[144,145]
	Other groups of drugs		
Mucolytics/antioxidants: - N-acetylcysteine	Precursor of the biological antioxidant glutathione, anti-inflammatory and antioxidant effect.	A decrease in scores on all three PANSS scales, an improvement on the CGI-S, CGI-I scales in patients with TRS. The reduction in negative symptom scores on the PANSS scale was more significant in patients with TRS.	[146,147]
Antibiotics: - Minocycline	Bacteriostatic action due to the suppression of protein synthesis by reversible binding to the 30S ribosomal subunit of sensitive microorganisms.	Decrease in scores on all three PANSS scales, improvement in BPRS scores, no changes in cognitive function in patients with TRS.	[148]
Polyunsaturated fatty acids: - Omega-3 fatty acids	Antioxidant, anti-inflammatory and neuroprotective effect.	Significant improvement on the three PANSS scales, as well as improvement in cognitive functions, was not revealed.	[149,150]

Note: BACS—Brief Assessment of Cognition in Schizophrenia; BPRS—Brief Psychiatric Rating Scale; CGI—Clinical

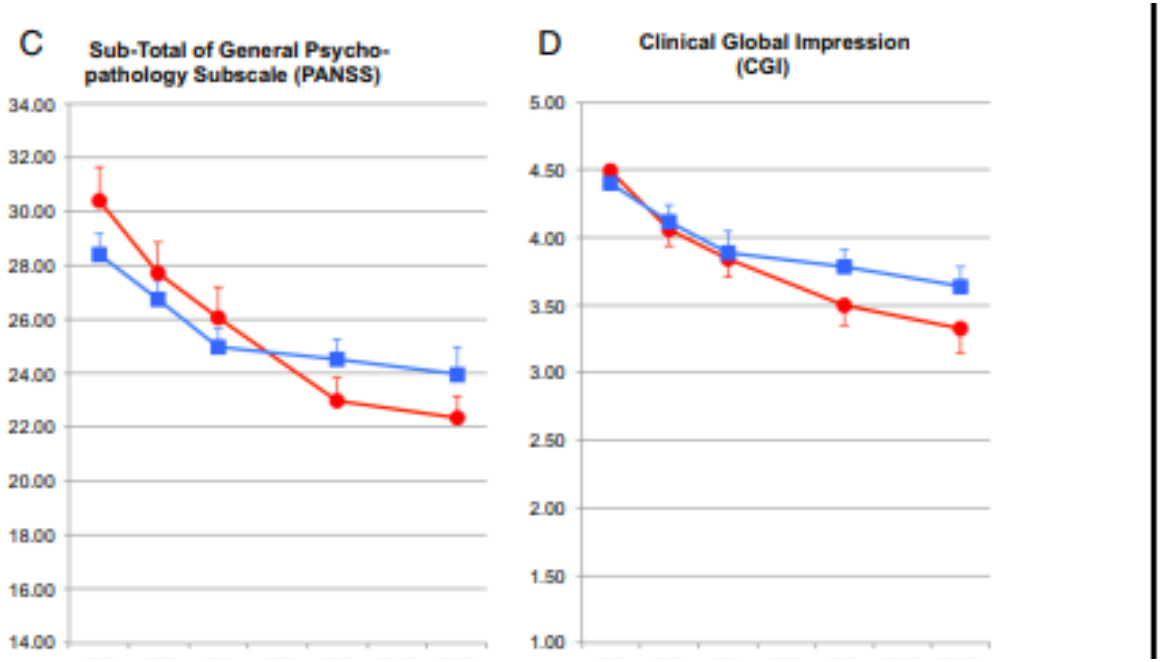
Chaudhry et al. *Translational Psychiatry* (2020)10:415
https://doi.org/10.1038/s41398-020-01095-8

Translational Psychiatry

ARTICLE Open Access

A randomised clinical trial of methotrexate points to possible efficacy and adaptive immune dysfunction in psychosis

I. B. Chaudhry[1,2,3], M. O. Husain[4,5,6], A. B. Khoso[6], M. I. Husain[4,5], M. H. Buch[7,8], T. Kiran[6], B. Fu[9], P. Bassett[10], I. Qurashi[11], R. ur Rahman[2], S. Baig[12], A. Kazmi[13], F. Corsi-Zuelli[14], P. M. Haddad[15], B. Deakin[1] and N. Husain[11]



a randomised, double blind, placebocontrolled exploratory trial of methotrexate 10 mg once a week added to TAU for patients with schizophrenia, schizoaffective disorder, psychosis not otherwise specified and schizophreniform disorder. Clinicaltrial.gov (NCT02074319) o

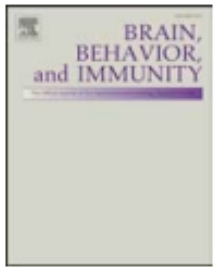
Antiinflamatórios em Psicose e Esquizofrenia

Brain, Behavior, and Immunity 90 (2020) 364–380

Contents lists available at ScienceDirect

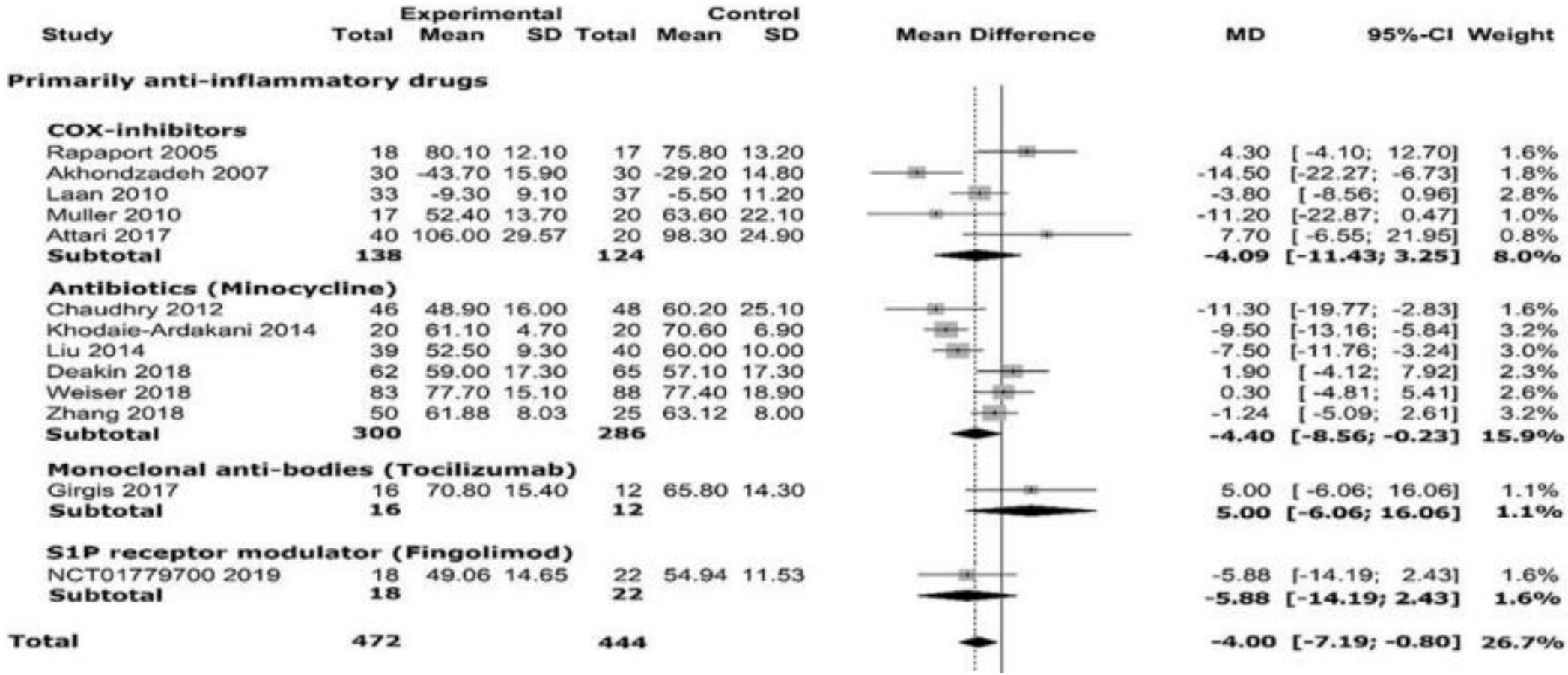
Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi



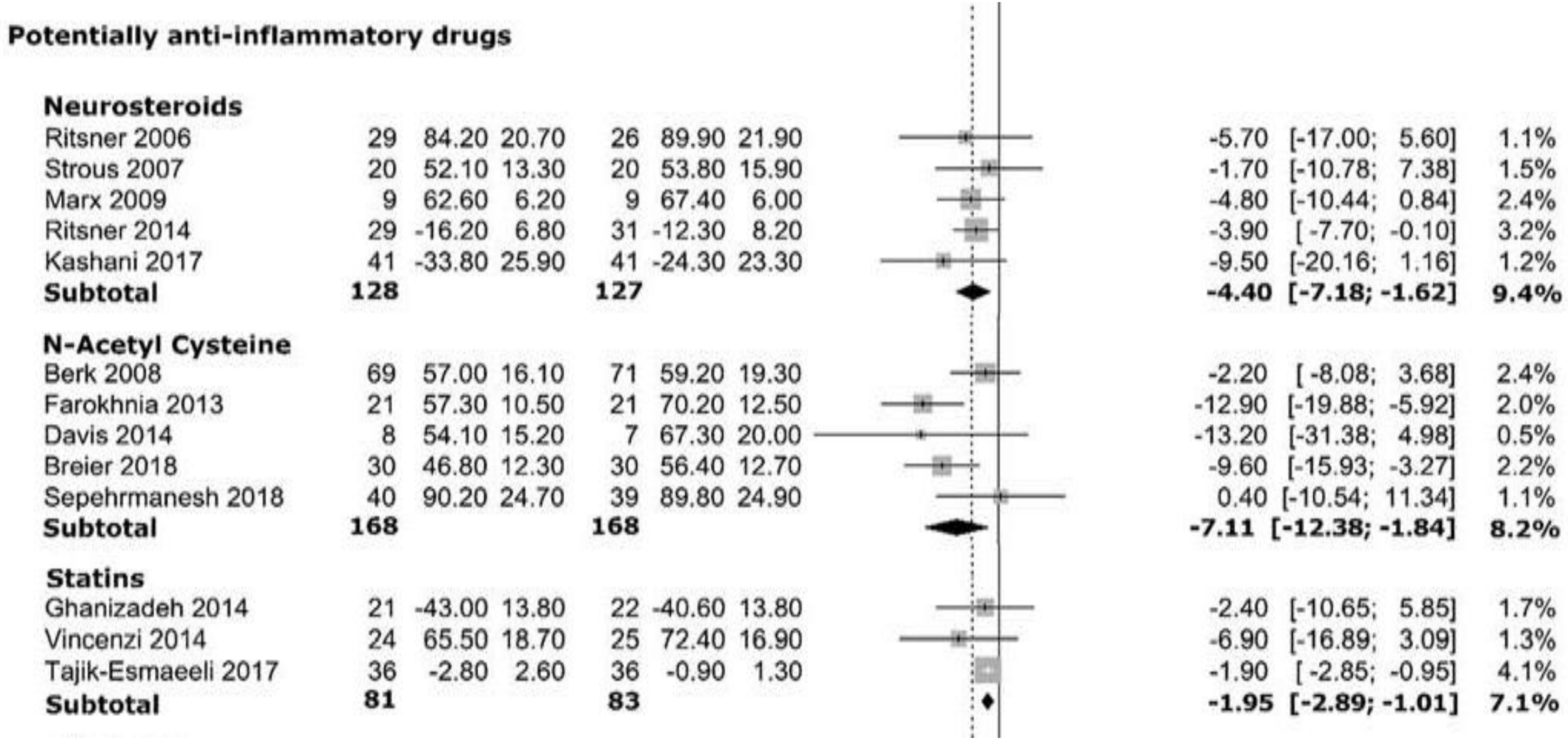
Efficacy and safety of anti-inflammatory agents in treatment of psychotic disorders – A comprehensive systematic review and meta-analysis

Rose Jeppesen[a], Rune H.B. Christensen[a], Emilie M.J. Pedersen[a], Merete Nordentoft[a,b], Carsten Hjorthøj[a,b,c], Ole Köhler-Forsberg[a,d,e], Michael E. Benros[a,f,*]



Study	Experimental Total	Mean	SD	Control Total	Mean	SD	MD	95%-CI	Weight
Primarily anti-inflammatory drugs									
COX-inhibitors									
Rapaport 2005	18	80.10	12.10	17	75.80	13.20	4.30	[-4.10; 12.70]	1.6%
Akhondzadeh 2007	30	-43.70	15.90	30	-29.20	14.80	-14.50	[-22.27; -6.73]	1.8%
Laan 2010	33	-9.30	9.10	37	-5.50	11.20	-3.80	[-8.56; 0.96]	2.8%
Muller 2010	17	52.40	13.70	20	63.60	22.10	-11.20	[-22.87; 0.47]	1.0%
Attari 2017	40	106.00	29.57	20	98.30	24.90	7.70	[-6.55; 21.95]	0.8%
Subtotal	**138**			**124**			**-4.09**	**[-11.43; 3.25]**	**8.0%**
Antibiotics (Minocycline)									
Chaudhry 2012	46	48.90	16.00	48	60.20	25.10	-11.30	[-19.77; -2.83]	1.6%
Khodaie-Ardakani 2014	20	61.10	4.70	20	70.60	6.90	-9.50	[-13.16; -5.84]	3.2%
Liu 2014	39	52.50	9.30	40	60.00	10.00	-7.50	[-11.76; -3.24]	3.0%
Deakin 2018	62	59.00	17.30	65	57.10	17.30	1.90	[-4.12; 7.92]	2.3%
Weiser 2018	83	77.70	15.10	88	77.40	18.90	0.30	[-4.81; 5.41]	2.6%
Zhang 2018	50	61.88	8.03	25	63.12	8.00	-1.24	[-5.09; 2.61]	3.2%
Subtotal	**300**			**286**			**-4.40**	**[-8.56; -0.23]**	**15.9%**
Monoclonal anti-bodies (Tocilizumab)									
Girgis 2017	16	70.80	15.40	12	65.80	14.30	5.00	[-6.06; 16.06]	1.1%
Subtotal	**16**			**12**			**5.00**	**[-6.06; 16.06]**	**1.1%**
S1P receptor modulator (Fingolimod)									
NCT01779700 2019	18	49.06	14.65	22	54.94	11.53	-5.88	[-14.19; 2.43]	1.6%
Subtotal	**18**			**22**			**-5.88**	**[-14.19; 2.43]**	**1.6%**
Total	**472**			**444**			**-4.00**	**[-7.19; -0.80]**	**26.7%**

Jeppesen et ali 2020



Jeppesen et ali 2020

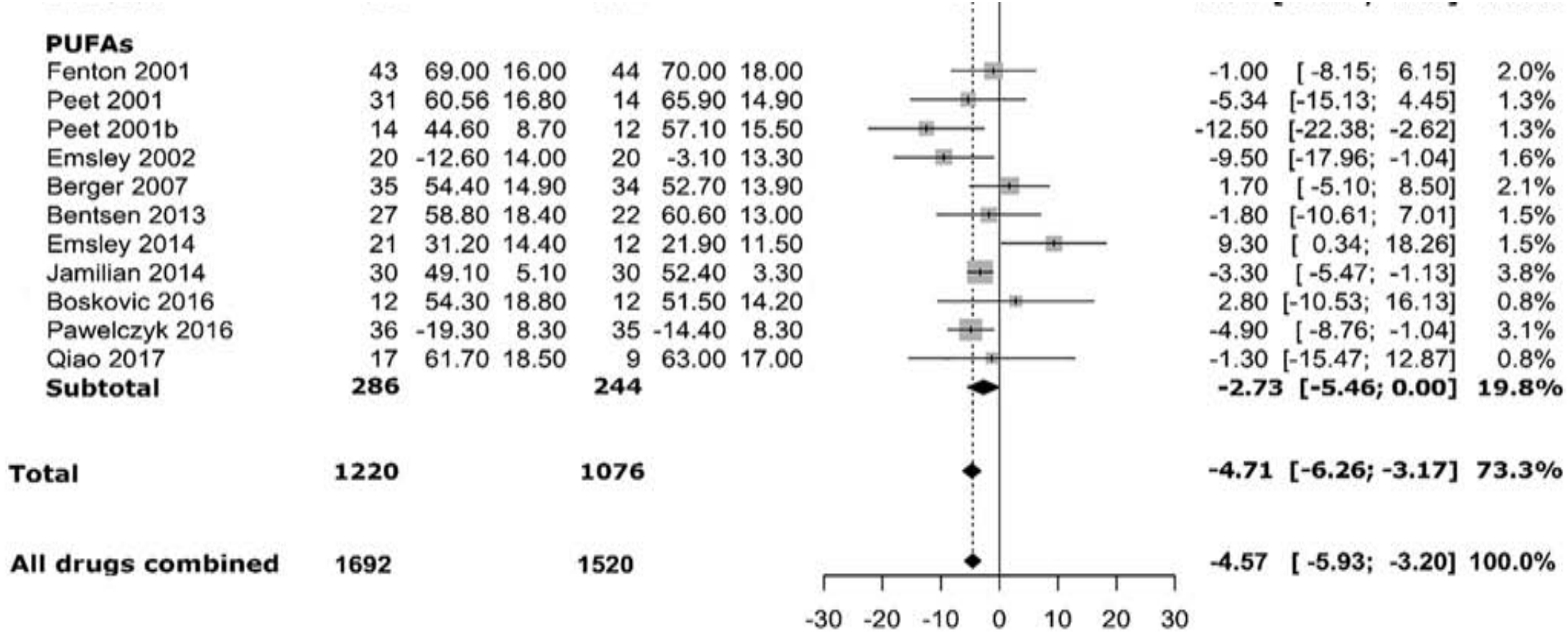
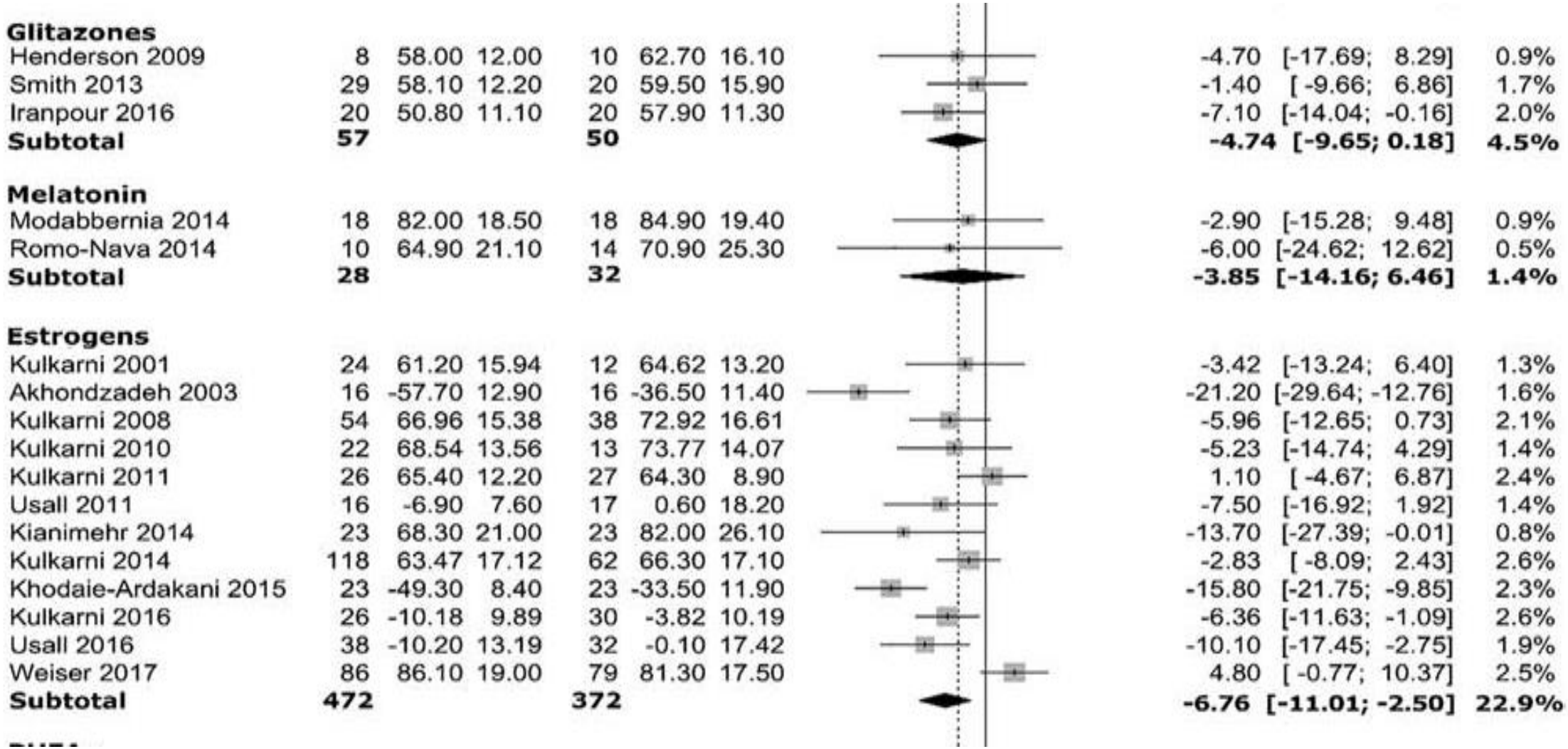


Fig. 2. Mean difference in PANSS total psychopathology score for anti-inflammatory add-on RCTs.

Jeppesen et ali 2020



Jeppesen et ali 2020

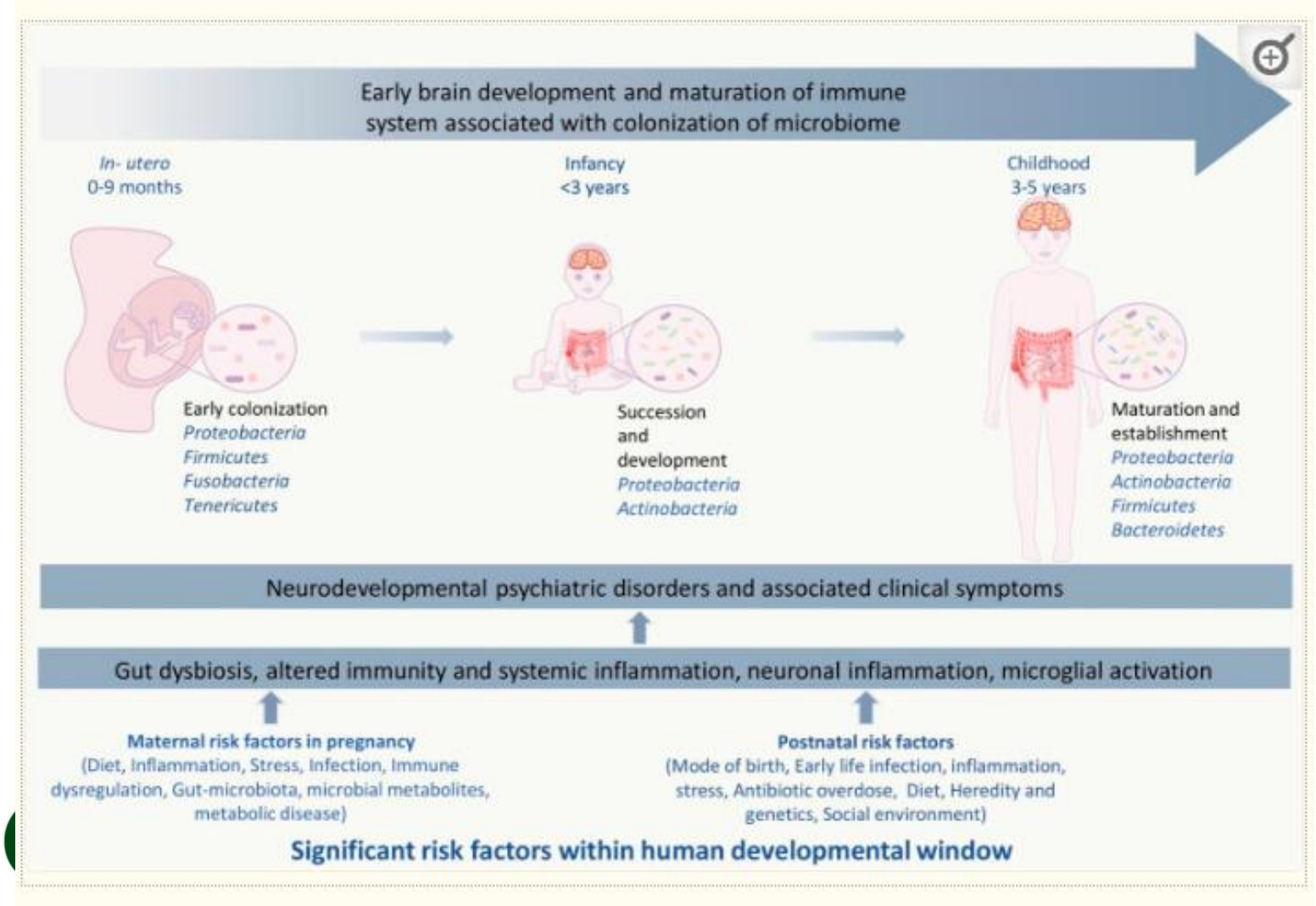
Limitações

- Pouco efeito sobre sintomas negativos e cognição
- número limitado de pacientes ou critério de seleção.
- Apenas um subgrupo de pacientes apresenta elevação da inflamação
- Marcadores variam de acordo com o estado da doença.
- IL-1 e IL-6 baixos durante a doença crônica estável
  - Aumentam em fase aguda,
- todos os pacientes selecionados estavam estáveis durante as três tentativas.
- Tocilizumab e Canakinumab mais indicados para psicose aguda.
- MAbs devem ser testados de acordo com o estado da doença, considerando pacientes agudamente doentes ou clinicamente estáveis como dois grupos separados em termos de perfil inflamatório

Jeppesen et ali 2020

Microbioma

Dash S, Syed YA, Khan MR. Understanding the Role of the Gut Microbiome in Brain Development and Its Association With Neurodevelopmental Psychiatric Disorders. Front Cell Dev Biol. 2022 Apr



Microbioma

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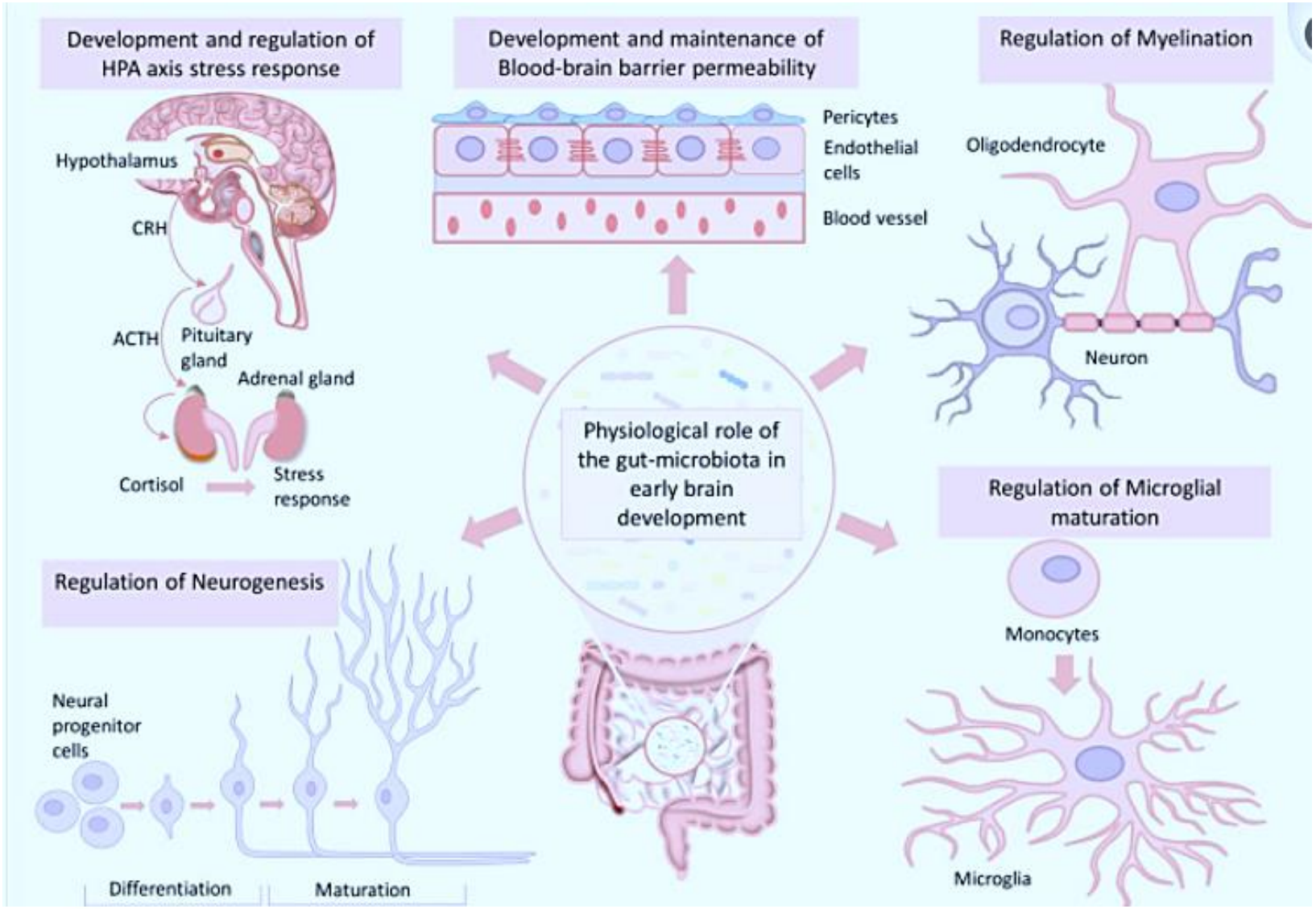


Microbioma

Dash S, Syed YA, Khan MR. Understanding the Role of the Gut Microbiome in Brain Development and Its Association With Neurodevelopmental Psychiatric Disorders. Front Cell Dev Biol. 2022 Apr

Neurodevelopmental disorders	Schizophrenia (SCZ)	
	Increased abundance	**Decreased abundance**
Gut microbiota	Phylum: *Proteobacteria* Genera: *Succinivibrio, Megasphaera, Collinsella, Clostridium, Klebsiella*, and *Methanobrevibacter* Shen et al. (2018)	*Coprococcus, Roseburia, Blautia* Shen et al. (2018)
		Phylum: *Proteobacteria*, Family: *Rumimococcaceae*, Genus: *Haemophilus, Sutterella, Clostridium* Nguyen et al. (2018)
	Anaerococcus, Bacteroids Nguyen et al. (2018)	
	Veillonella atypica, Veillonella dispar, Bifidobacterium dentium, Dialister invisus, Lactobacillus oris, Streptococcus salivarius, Lactobacillus fermentum, Enterococcus faecium, Alkaliphilus oremlandii, and *Cronobacter sakazakii/turicensis* Zhu et al., (2020a)	*Bifidobacterium, E. coli*, and *Lactobacillus* Cuomo et al. (2018) *Bifidobacterium longum* Katz-Barber et al. (2020) *Rhodocyclales, Enterococcaceae, Rikenellaceae, Alcaligenaceae, Rhodocyclaceae, Leuconostocaceae, Enterococcus* Xu et al. (2019)
	Taxa: *Lactobacillaceae, Lachnospiraceae, Veillonellaceae* Schwarz et al. (2018); Zheng et al. (2019)	Family: *Erysipelotrichaceae*, genus: *Allobaculum* Gubert et al. (2020)
	Clostridiales, Lactobacillales, Bacteroidales de Angelis et al. (2013); Shen et al. (2018)	
	Akkermansia muciniphila, Bacteroides plebeius, Veillonella parvula, Clostridium symbiosum, Eubacterium siraeum, Cronobacter sakazakii/turicensis, S. vestibularis, Alkaliphilus oremlandii, Enterococcus faecium, Bifidobacterium longum, Bifidobacterium adolescentis (Zhu et al., 2020a)	
	Deltaproteobacteria, Actinobacteria, Sphingomonadales, Actinomycetales, Sphingomonadaceae, Megasphaera, Eggerthella and, *Megasphaera elsdeniis, Clostridium perfringens, Akkermansia, muciniphila, Lactobacillus gasseri, and Bifidobacterium adolescentis* Xu et al. (2019)	
	Acidaminococcus, Akkermansia, Alistipes, Citrobacter, Dialister, Veillonella Zheng et al. (2019)	
Cytokines levels	C4A Stevens et al. (2007); Schafer et al. (2012); S.; Hong et al. (2016); Comer et al. (2020)	IL-1β, IL-10 Delaney et al. (2019); Park and Miller, (2020); Perkins et al. (2015)
	C-reactive protein (CRP) Prins et al. (2016); Ligthart et al. (2018)	IL-17 Zeni-Graiff et al. (2016)

Glucorafanina → Sulforafane

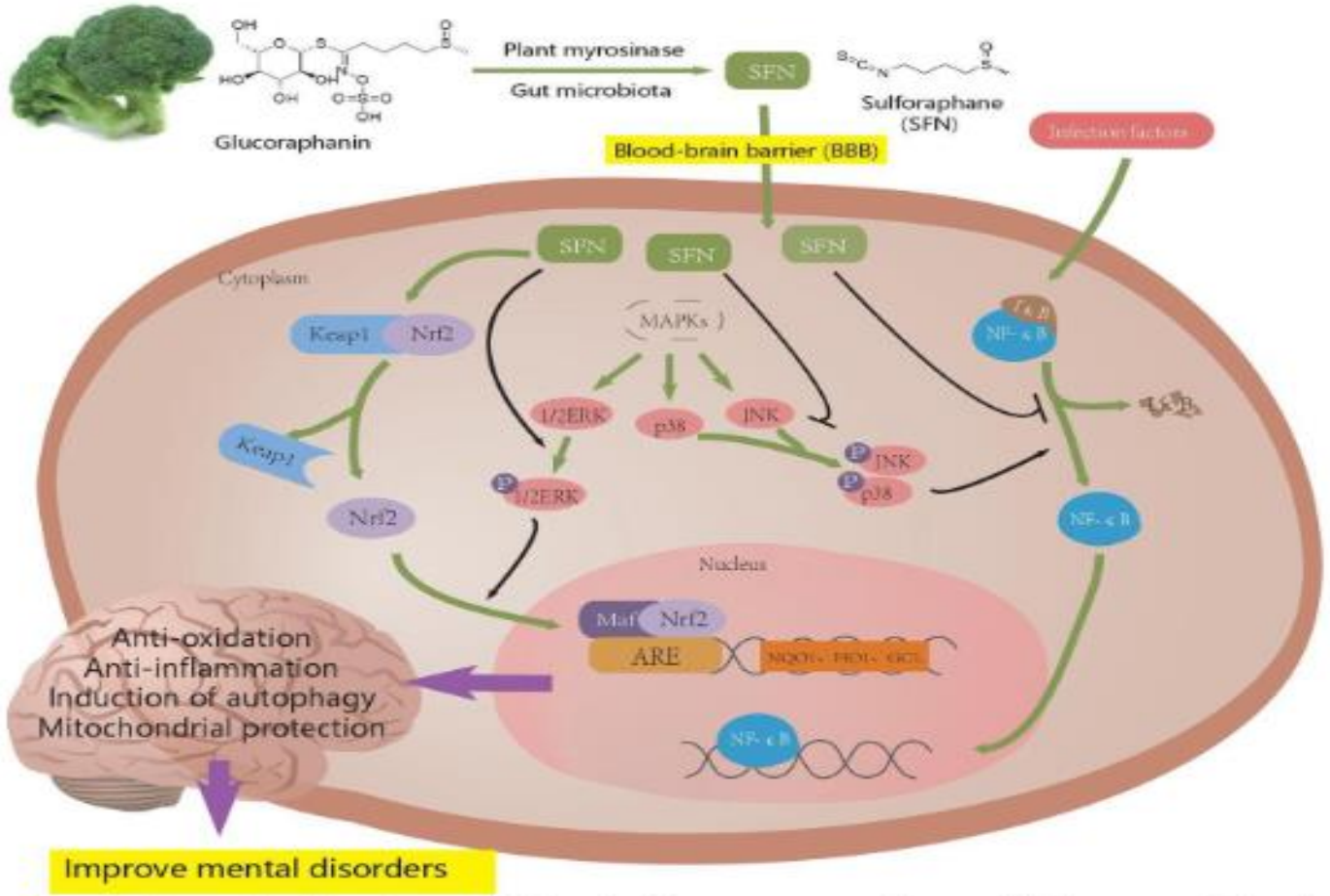


Figure 1 Biological mechanisms of sulforaphane. ARE, antioxidant response element; ERK, extracellular signal-regulated kinase; GCL, glutamate cysteine ligase; HO1, haem oxygenase 1; IκB, inhibitor of NF-κB; JNK, c-Jun N-terminal kinase; Keap1, Kelch-like ECH-associated protein 1; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; NQO1, NAD(P)H quinone dehydrogenase 1; Nrf2, nuclear factor erythroid 2-related factor 2.

CENTRO DE ESTUDOS DE LITERATURA E PSICANÁLISE CYRO MARTINS

Zheng W, Li X, Zhang T, et al. Biological mechanisms and clinical efficacy of sulforaphane for mental disorders. General Psychiatry2022;35:e100700. doi:10.1136/gpsych-2021-10070

- Schizophrenia, Shiina(2015)Open-label study, 20–65years.SFN (n=7) 30mg/day.8weeks.
  - After SFN treatment, the mean scores in the OCLT showed a significant increase from 0.88 to 0.95 (p=0.043).
- Schizophrenia, Dickerson (2021) RCT, 18–65years.SFN (n=29), placebo (n=29)
  - 100µmol/day.18weeks
  - No significant difference in psychiatric symptoms or cognitive function

  - OCLT, One Card Learning Task; RCT, randomised clinical trials; SFN, sulforaphane; SRS, Social Responsiveness Scale

ALVOS ATUAIS E FUTUROS DE ANTIPSICÓTICOS

Pharmacological Research 176 (2022) 106078

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

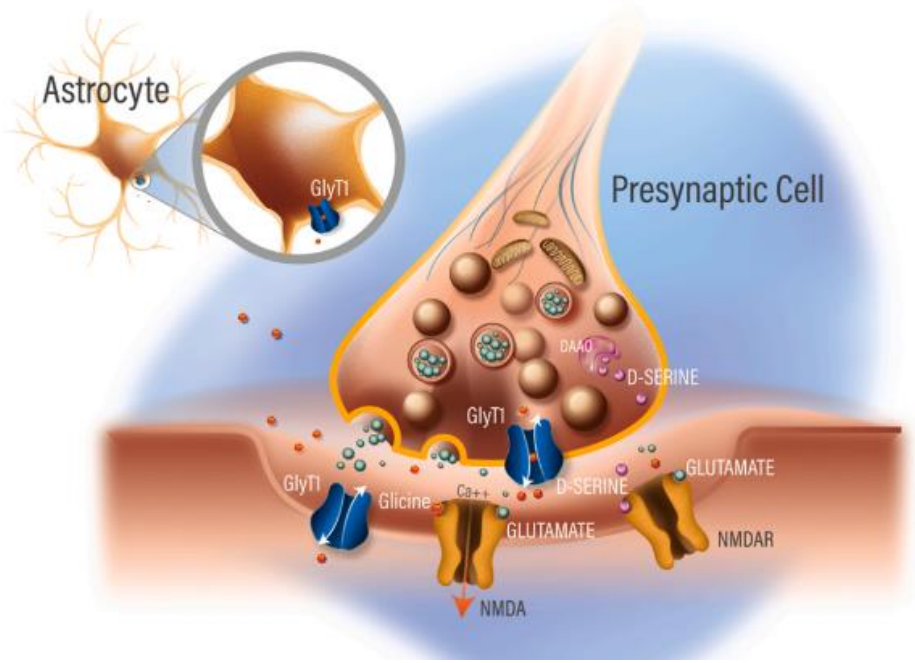
Review

Present and future antipsychotic drugs: A systematic review of the putative mechanisms of action for efficacy and a critical appraisal under a translational perspective

Andrea de Bartolomeis [a,*], Annarita Barone [a], Veronica Begni [b], Marco Andrea Riva [b,c,**]

Receptor	APs action	Putative target symptoms
D1	agonism	negative symptoms
D2	antagonism/partial agonism	positive symptoms
D3	antagonism/partial agonism	cognitive and negative symptoms
D4	antagonism	cognitive and negative symptoms
5-HT1A	agonism	cognitive, anxiety and depressive symptoms
5-HT2A	antagonism	negative symptoms
5-HT7	antagonism	cognitive, anxiety and depressive symptoms
α7nACh	agonism	cognitive symptoms
AchMR1/4	agonism	positive and negative symptoms
H1	antagonism	agitation, anxiety symptoms
α1	antagonism	positive symptoms
α_{2c}	antagonism	cognitive, negative and depressive symptoms
mGluR2/3	agonism and allosteric modulation	cognitive symptoms
σ_1	antagonism	negative symptoms
TAAR1	agonism	positive, negative and cognitive symptoms

de Bartolomeis, 2022



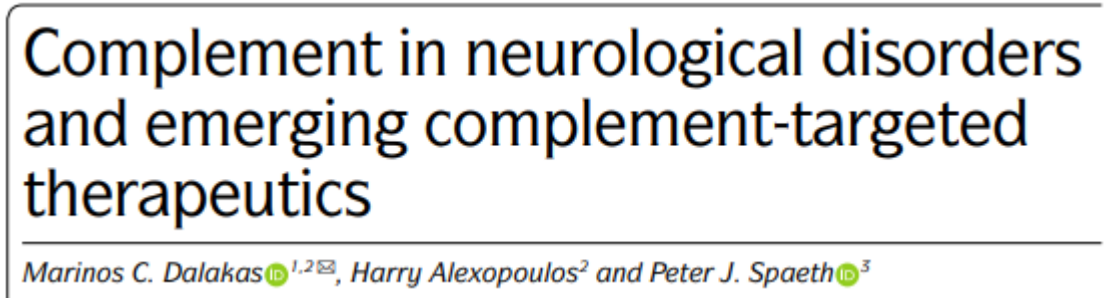
Novos alvos potenciais de antipsicóticos
GlyT1 remove glicina da fenda sináptica e transportando-a dentro das células.

hipofunção NMDAR → + glicina inibindo GlyT1 ++NMDAR
inibição da enzima DAO (responsável pela degradação da D-serina). DAO inativada: D-serina aumenta na fenda sináptica aumento Funcionamento NMDAR.

GlyT1: de Receptor de Glicina 1; NMDAR: NTransportador-receptores de metil-D-aspartato; DAO: D-aminoácido oxidase.

de Bartolomeis, 2022

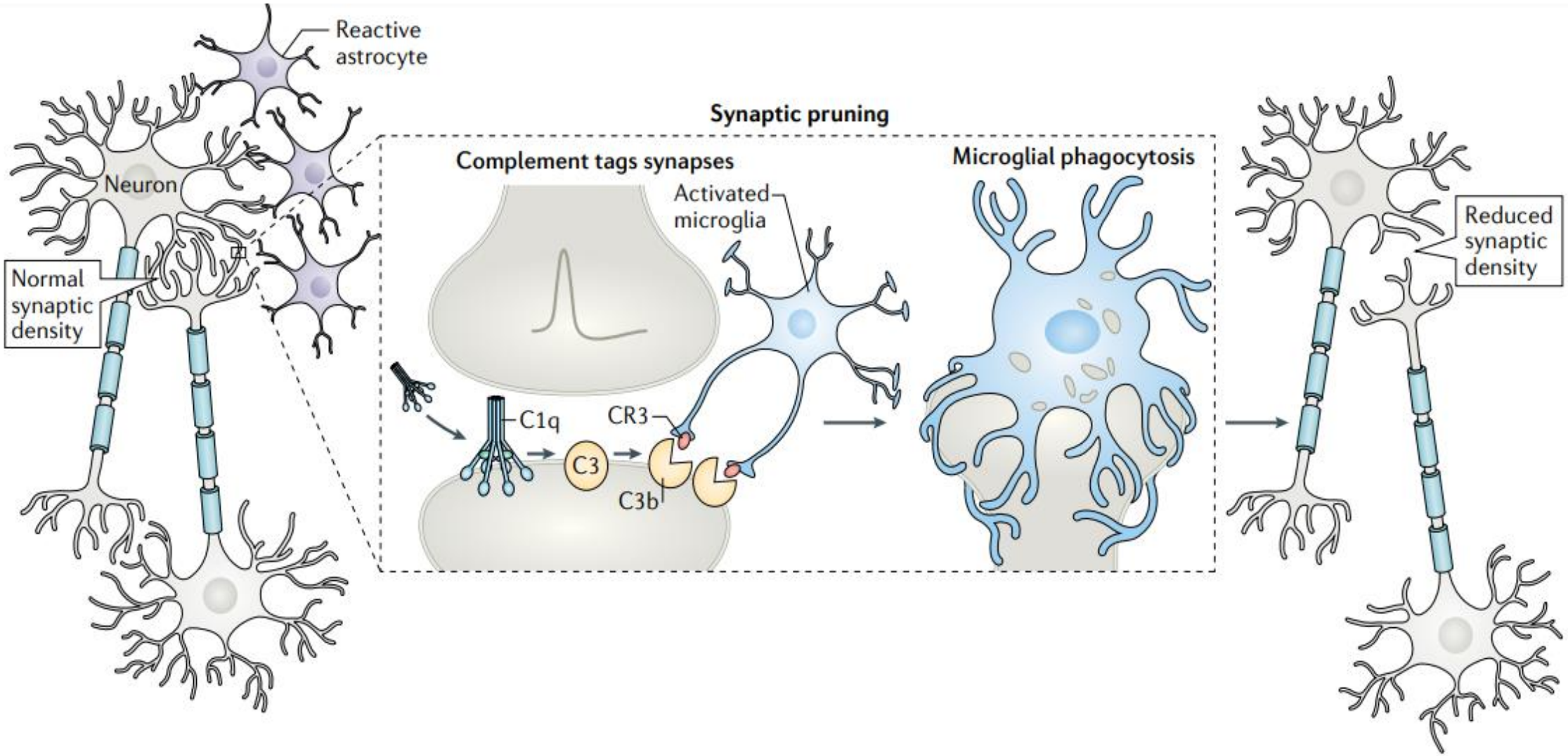
- Sistema Complemento em Esquizofrenia



Complement in neurological disorders and emerging complement-targeted therapeutics

Marinos C. Dalakas[1,2]✉, Harry Alexopoulos[2] and Peter J. Spaeth[3]

Nature Reviews | Neurology volume 16 | November 2020 | 601



Nature Reviews | Neurology volume 16 | November 2020 | 601

nature communications

Article

https://doi.org/10.1038/s41467-022-33797-6

Cerebrospinal fluid concentration of complement component 4A is increased in first episode schizophrenia

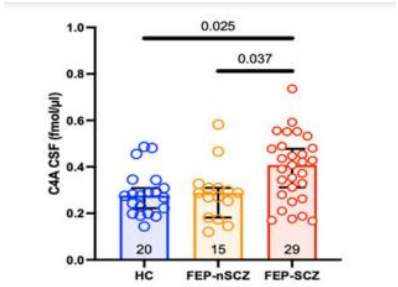
Received: 2 September 2021

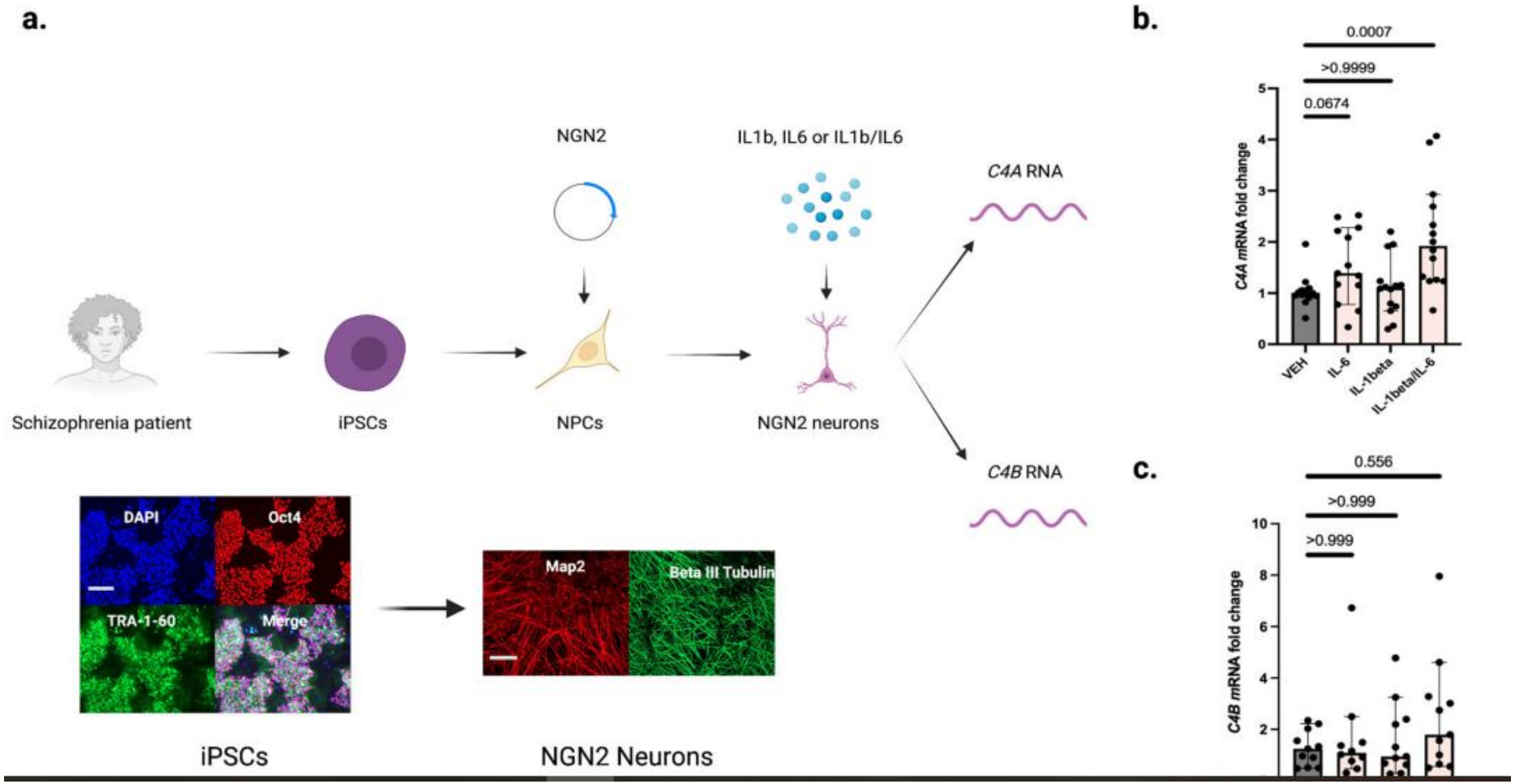
Accepted: 3 October 2022

Published online: 03 November 2022

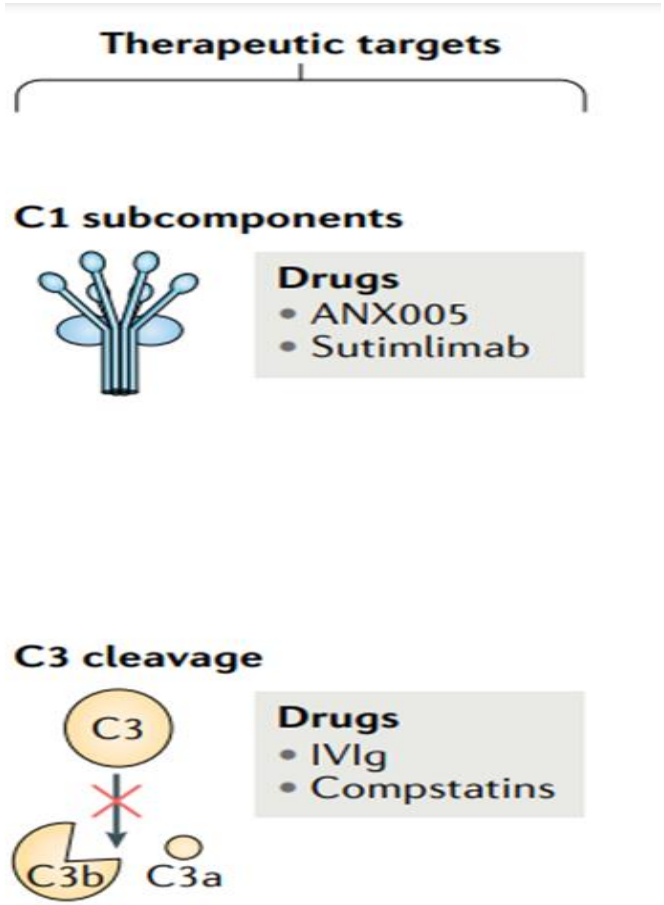
Check for updates

Jessica Gracias[1], Funda Orhan[1], Elin Hörbeck[2,3], Jessica Holmén-Larsson[2], Neda Khanlarkani[1], Susmita Malwade[1], Sravan K. Goparaju[1], Lilly Schwieler[1], İlknur Ş. Demirel[1], Ting Fu[4], Helena Fatourus-Bergman[5,6], Aurimantas Pelanis[7], Carleton P. Goold[8], Anneli Goulding[3,9], Kristina Annerbrink[3], Anniella Isgren[2,3], Timea Sparding[2], Martin Schalling[10], Viviana A. Carcamo Yañez[11], Jens C. Göpfert[11], Johanna Nilsson[2], Ann Brinkmalm[2], Kaj Blennow[2,12], Henrik Zetterberg[2,12,13,14,15], Göran Engberg[1], Fredrik Piehl[5], Steven D. Sheridan[4], Roy H. Perlis[4], Simon Cervenka[5,6,16], Sophie Erhardt[1], Mikael Landen[2,17] & Carl M. Sellgren[1,6]





Nature Communications | (2022) 13:6427


Therapeutic targets
C1 subcomponents
Drugs
• ANX005
• Sutimlimab
C3 cleavage
C3
C3b
C3a
Drugs
• IVIg
• Compstatins
C5 cleavage
C5
C5b
C5a
Drugs
• Eculizumab
• Ravulizumab
• Zilucoplan
• Tesidolumab
• SKY59

Neuromodulação
Esquizofrenia

Brain Stimulation 14 (2021) 1393–1403

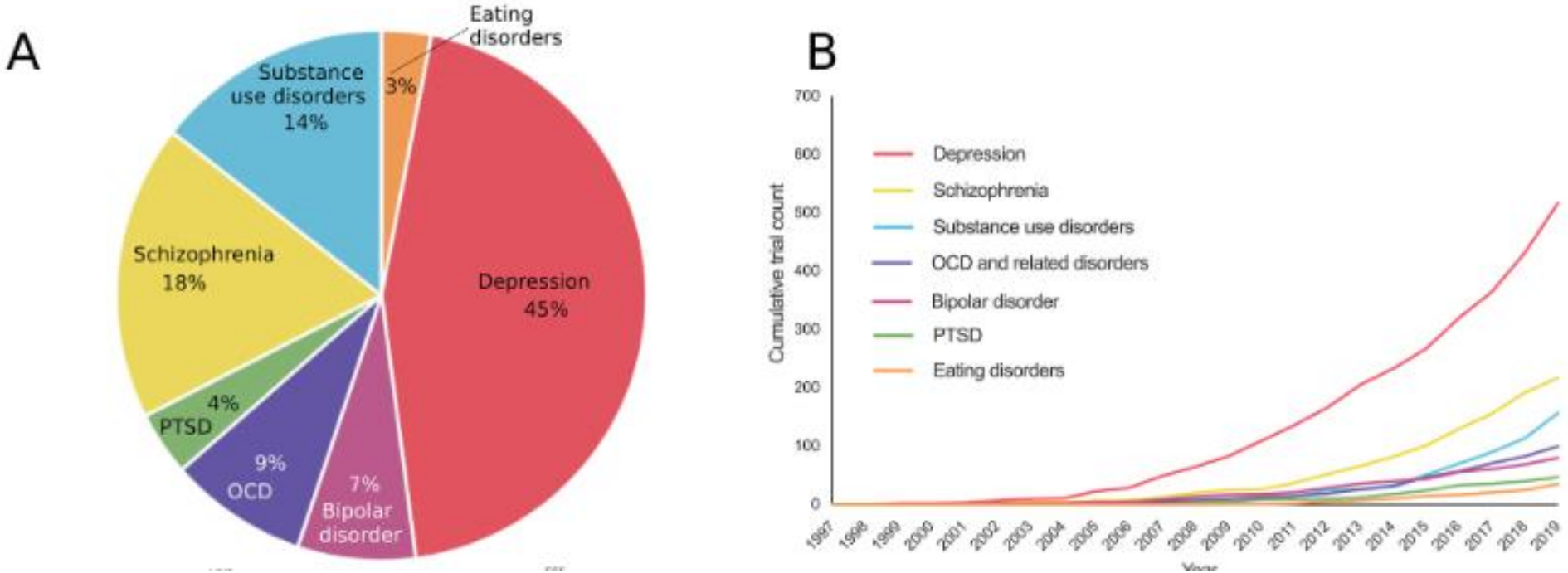
Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Neuromodulatory treatments for psychiatric disease: A comprehensive survey of the clinical trial landscape

Gavin J.B. Elias [a, b, 1], Alexandre Boutet [a, b, c, 1], Roohie Parmar [a], Emily H.Y. Wong [a], Jürgen Germann [a, b], Aaron Loh [a, b], Michelle Paff [a], Aditya Pancholi [a], Dave Gwun [a], Clement T. Chow [a], Flavia Venetucci Gouveia [d], Irene E. Harmsen [a, b], Michelle E. Beyn [a], Emiliano Santarnecchi [e], Alfonso Fasano [b, f, g], Daniel M. Blumberger [h, i], Sidney H. Kennedy [b, i, j], Andres M. Lozano [a, b], Venkat Bhat [b, i, j, *]



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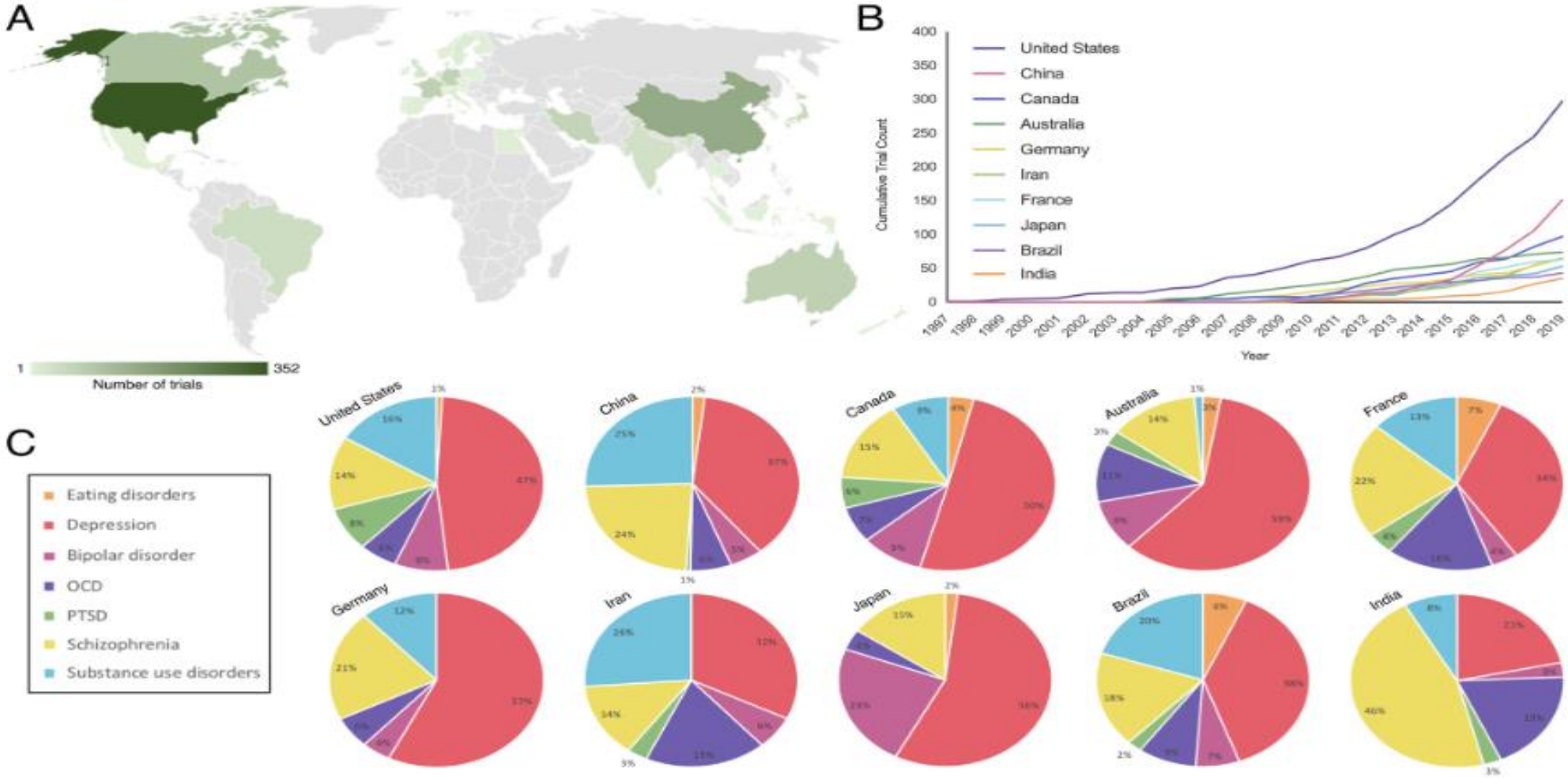


ECT

International Journal of *Molecular Sciences*

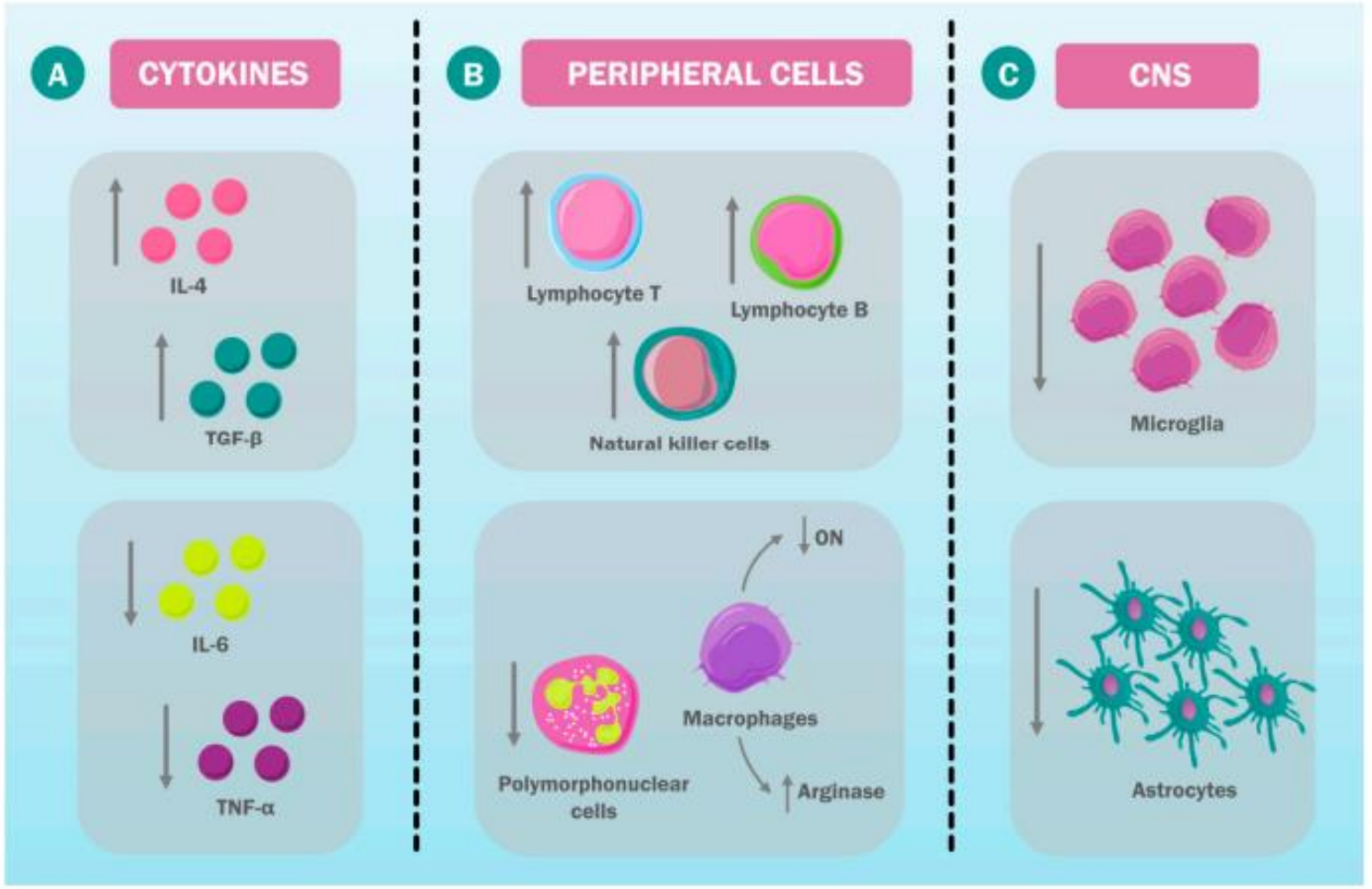
MDPI

Review

Electroconvulsive Therapy in Psychiatric Disorders: A Narrative Review Exploring Neuroendocrine–Immune Therapeutic Mechanisms and Clinical Implications

Milagros Rojas [1,*], Daniela Ariza [1], Ángel Ortega [1], Manuel E. Riaño-Garzón [2], Mervin Chávez-Castillo [1,3], José Luis Pérez [1], Lorena Cudris-Torres [4], María Judith Bautista [2], Oscar Medina-Ortiz [5,6], Joselyn Rojas-Quintero [7] and Valmore Bermúdez [6,*]

Efeitos Imunológicos de ECT



Rojas et ali 2022

frontiers in Neurology

ORIGINAL RESEARCH
published: 15 December 2021
doi: 10.3389/fneur.2021.766736

Potential Locations for Non-Invasive Brain Stimulation in Treating Schizophrenia: A Resting-State Functional Connectivity Analysis

Yanzhe Ning [1,2†], Sisi Zheng [1,2†], Sitong Feng [1,2], Binlong Zhang [3] and Hongxiao Jia [1,2*]*

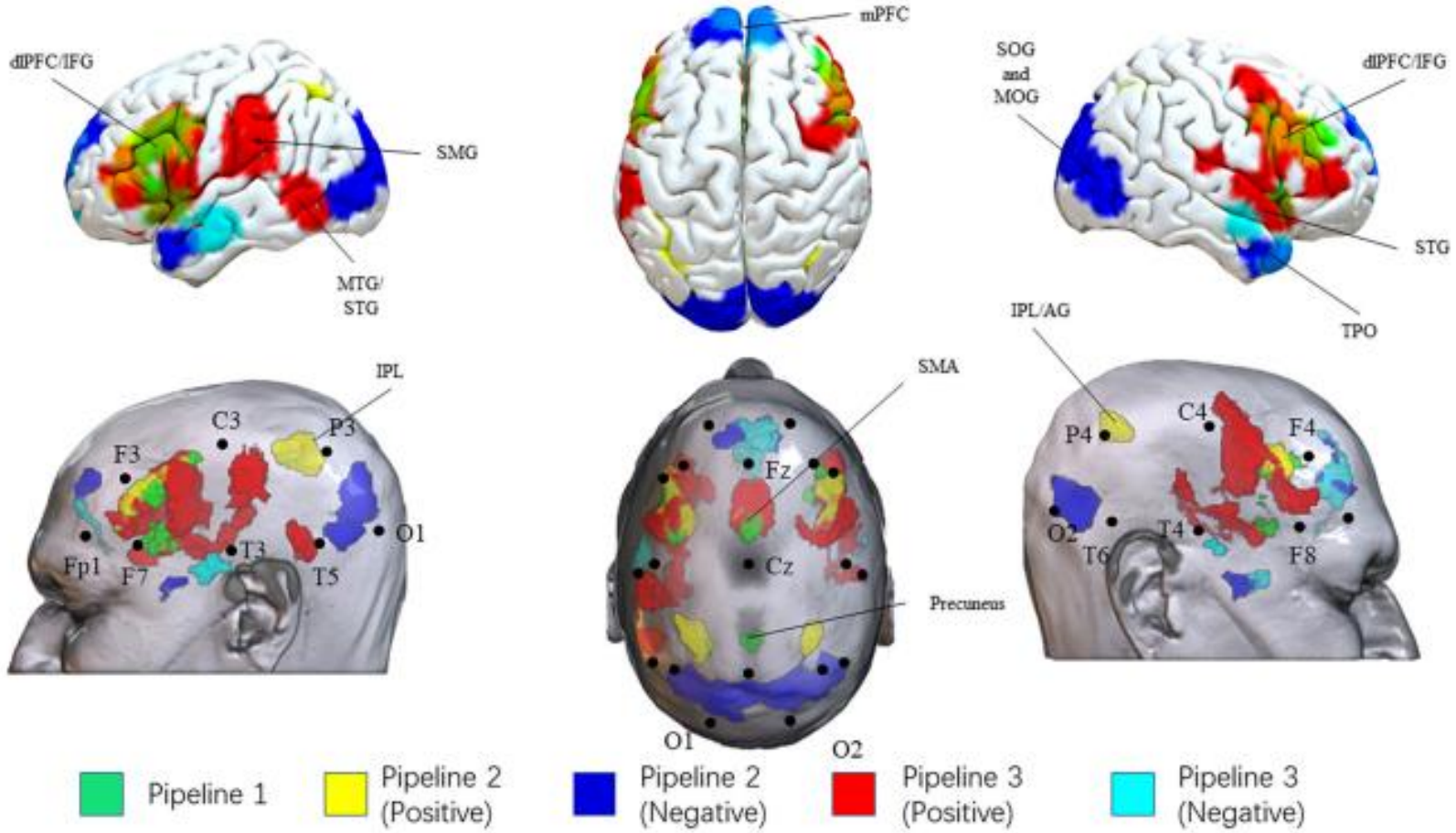


FIGURE 2 | Results of three pipelines. Brain surface regions identified from the three pipelines were presented on the top. Scalp locations corresponding to the brain surface regions were presented on the bottom. Results from pipeline 1, pipeline 2 (positive correlation), pipeline 2 (negative correlation), pipeline 3 (positive correlation), pipeline 3 (negative correlation) were presented as green, yellow, blue, red, and cyan, respectively. L, left; R, right; IPL, Inferior Parietal Lobule; AG, angular gyrus; SMG, supramarginal gyrus SMA, supplementary motor area; dlPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; mPFC, medial prefrontal cortex; MTG, middle temporal gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; TPO, temporal pole; SOG, superior occipital gyrus; MOG, middle occipital gyrus.

Estimulação Transcraniana - tdcs

in Behavioral Neuroscience

REVIEW
published: 25 May 2022
doi: 10.3389/fnbeh.2022.893955

Check for updates

Transcranial Direct Current Stimulation of the Dorsolateral Prefrontal Cortex for Treatment of Neuropsychiatric Disorders

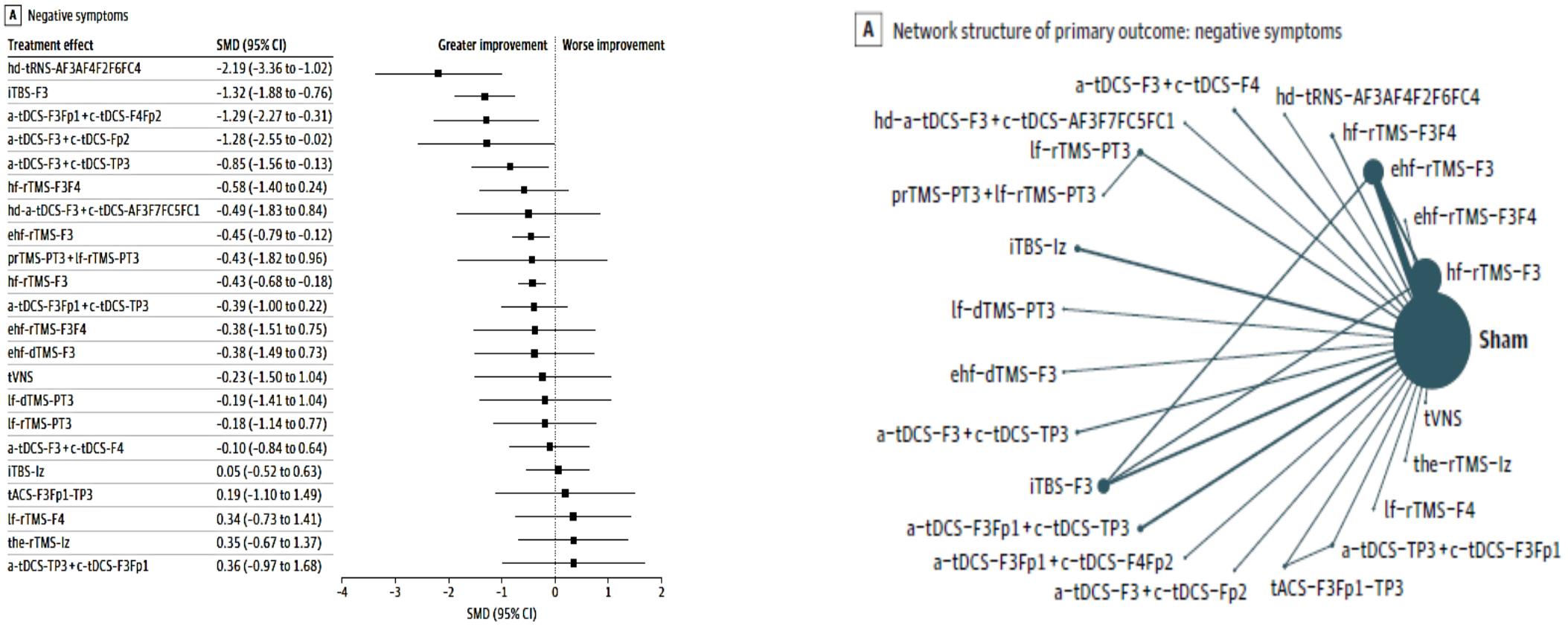
Qing Li[1,2], Yu Fu[1], Chang Liu[3,4,5] and Zhiqiang Meng[2,4,5]**

JAMA Psychiatry | Original Investigation

Assessment of Noninvasive Brain Stimulation Interventions for Negative Symptoms of Schizophrenia

A Systematic Review and Network Meta-analysis

Ping-Tao Tseng, MD, PhD; Bing-Syuan Zeng, MD; Chao-Ming Hung, MD, PhD; Chih-Sung Liang, MD; Brendon Stubbs, MD, PhD;



NIBS excitatória (Randon Noise-estimulação de ruído transcraniano aleatório, iTBS (theta-burst intermitente), tdcs (estimulação transcraniana por corrente contínua, EMT/TMS (estimulação magnética repetitiva transcraniana) córtex pré-frontal dorsolateral Esquerdo com/sem estimulação regiões cerebrais contralaterais: redução de sintomas negativos X sham (placebo). Aceitabilidade =

O Futuro

Caminhos para descoberta de novas drogas em Esquizofrenia

Proteômica em SCZ

European Neuropsychopharmacology 61 (2022) 43-59

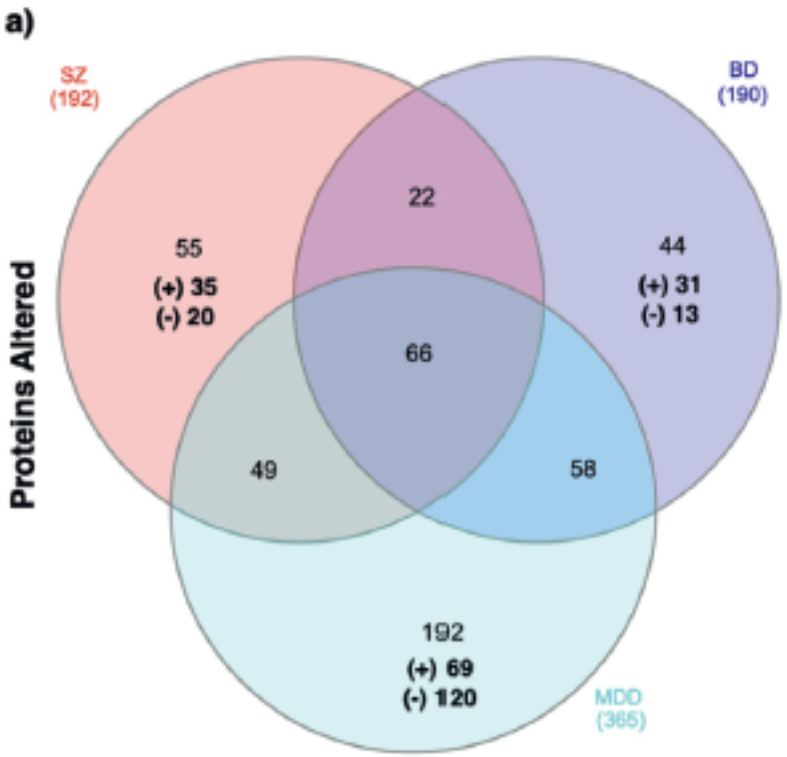
ELSEVIER

www.elsevier.com/locate/euroneuro

Charting the proteome landscape in major psychiatric disorders: From biomarkers to biological pathways towards drug discovery

Brisa S. Fernandes[a], Yulin Dai[a], Peilin Jia[a], Zhongming Zhao[a,b,c,d,*]

European Neuropsychopharmacology 61 (2022) 43-59



Decreased SZ and Increased BD and MDD (10)
Carbonic anhydrase 1 (CAH1)
Tetranectin (TETN)
Apolipoprotein D (APOD)
Interleukin-17A (IL17)
Vitamin D-binding protein (VTDB)
Interleukin-10 (IL10)
Interleukin-12 subunit beta (IL12B)
Apolipoprotein C-I (APOC1)
Apolipoprotein C-II (APOC2)
Apolipoprotein C-III (APOC3)

Increased SZ and Decreased BD and MDD (3)
C-C motif chemokine 5 (CCL5)
Kit ligand (SCF)
Growth-regulated alpha protein (GROA)

Decreased SZ and BD and Increased MDD (4)
Angiotensin-Converting Enzyme (ACE)
Interleukin-13 (IL13)
Stromelysin-1 (MMP3)
Apolipoprotein A-II (APOA2)

Increased SZ and BD and Decreased MDD (8)
Pro-epidermal growth factor (EGF)
Antithrombin III (ANT3)
C-C motif chemokine 4 (CCL4)
Insulin-like growth factor-binding protein 2 (IBP2)
Cystatin-C (CYTC)
Glycoprotein hormones alpha chain (GLHA)
Chromogranin-A (CMGA)
Thyrotropin subunit beta (TSHB)

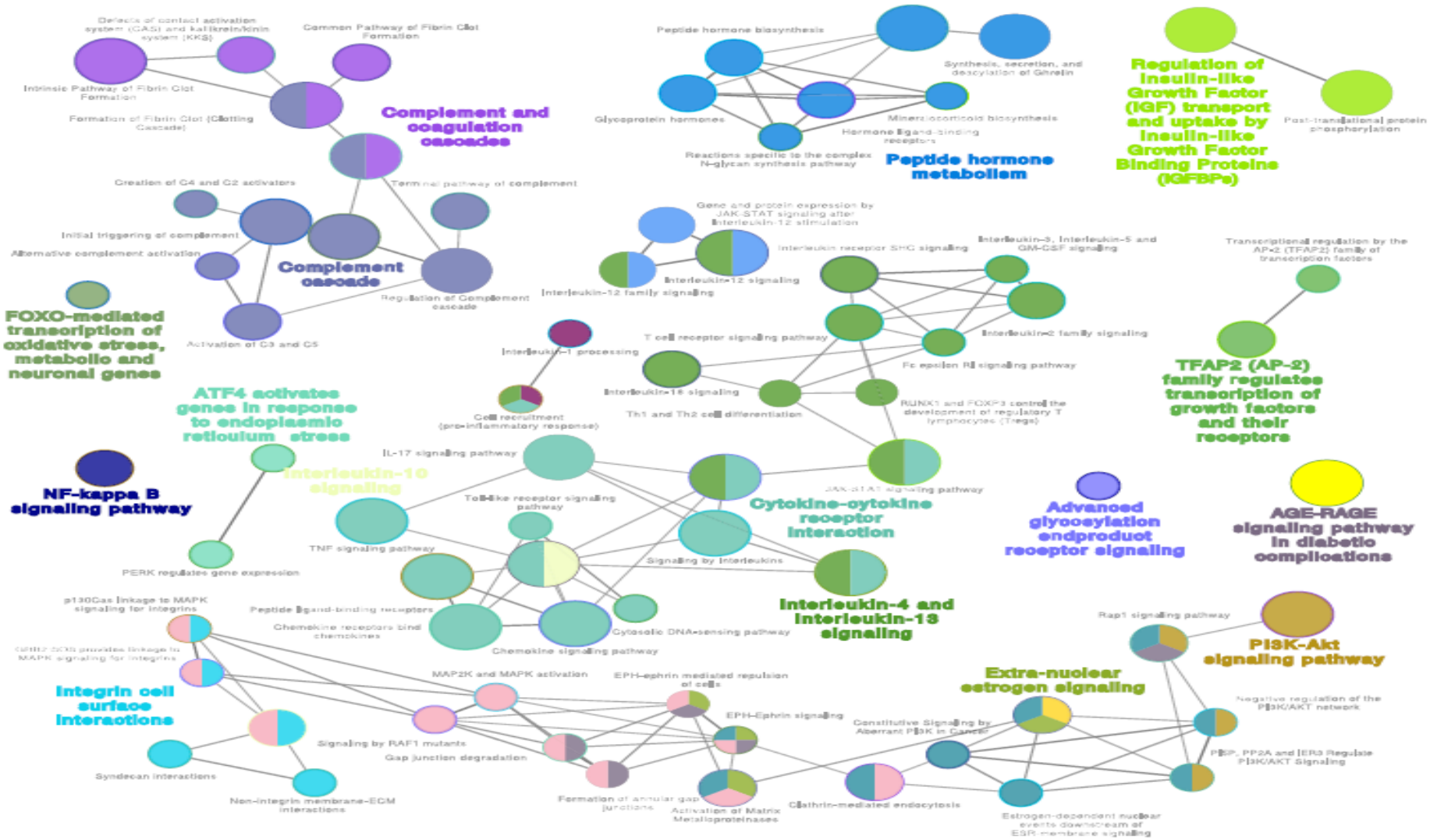


Fig. 2 Pathway network in schizophrenia.

Desafios para novos tratamentos

Desafios no desenvolvimento e uso de antinflamatórios e anticitocinas para psicose

- aumentar evidência de impacto direto da inflamação na estrutura e função do cérebro em abordagem transdiagnóstica em estágios iniciais de distúrbios
  - Krynicki et al.,2021; Williams et al., 2022
- Entender quem se beneficiaria de um anti-inflamatório
  - fenótipo da psicose imunoativa ativa
  - estratificar a psicose com indicação de imunoterapia:
    - Sintomas, biomarcadores
    - Desfecho primário: sintomas negativos, anedonia ou funcionamento geral
- Psychosis Immune Mechanism Stratified Medicine Study (PIMS)

Advanced Drug Delivery Reviews 191 (2022) 114564

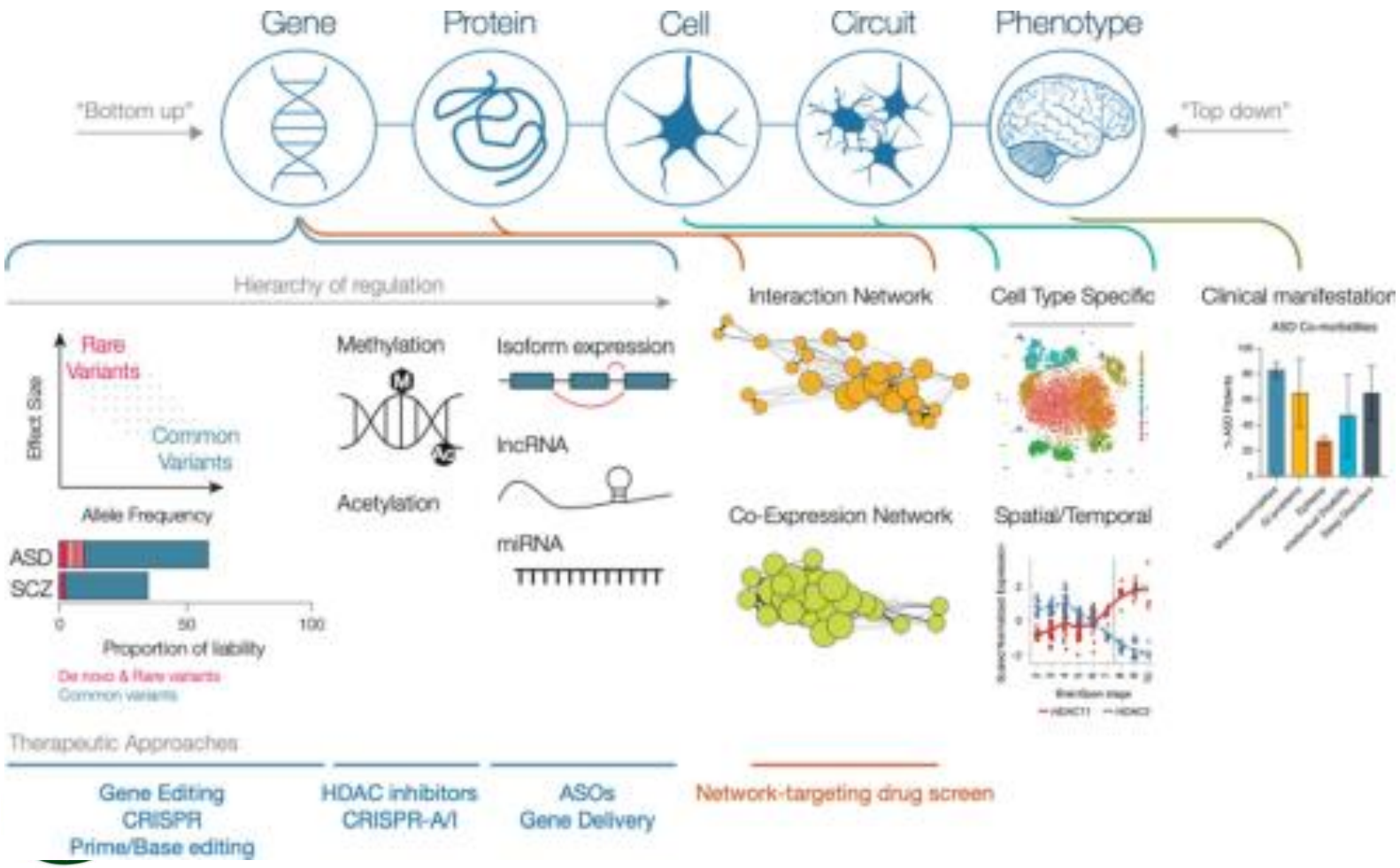
Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/adr

Challenges and opportunities for precision medicine in neurodevelopmental disorders

George T. Chen [a,b], Daniel H. Geschwind [a,b,c,d,e,*]



Advanced Drug Delivery Reviews 191 (2022) 114564

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/adr

Challenges and opportunities for precision medicine in neurodevelopmental disorders

George T. Chen [a,b], Daniel H. Geschwind [a,b,c,d,e,*]

iPSC-derived SCZ neurons	Immunoprecipitation	SCZ-perturbed genes are downregulated in layer 5/6 cortical neurons
Postmortem ASD, BD, SCZ, and neurotypical brain	Bulk RNA, Microarray	Disease-specific and shared expression modules; Shared modules include increased inflammation and excitatory neuron signaling

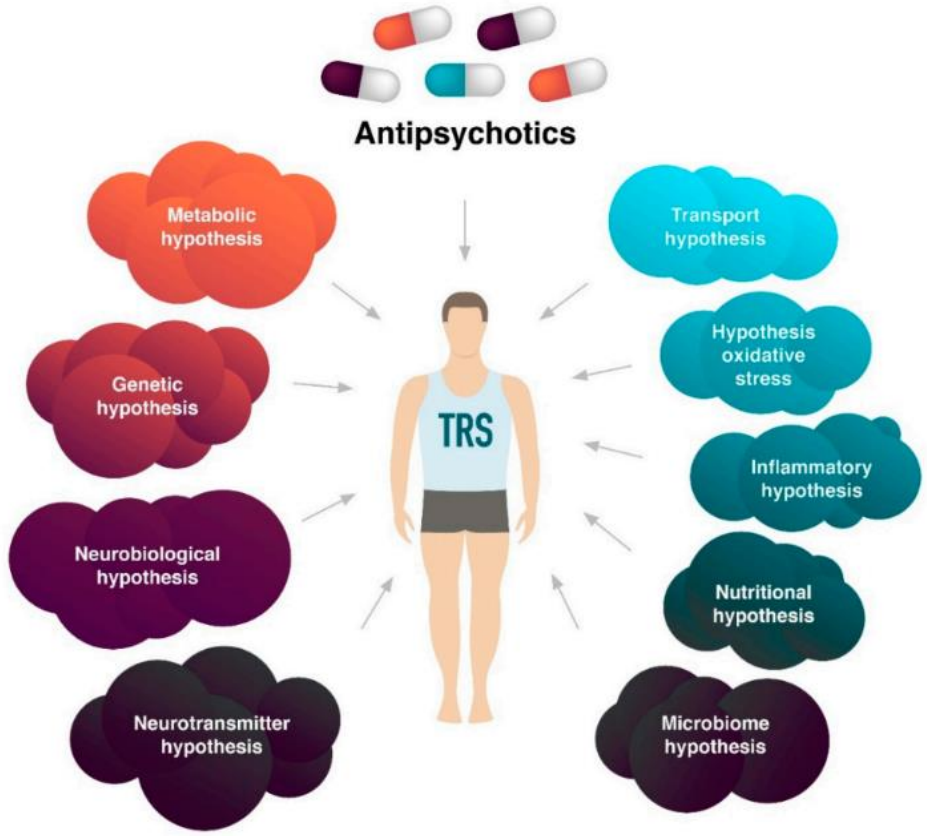
Alteração da regulação (--) neurônios corticais camada 5/6
Alteração de módulos de genes relacionados a inflamação e transmissão de sinal excitatório (++)

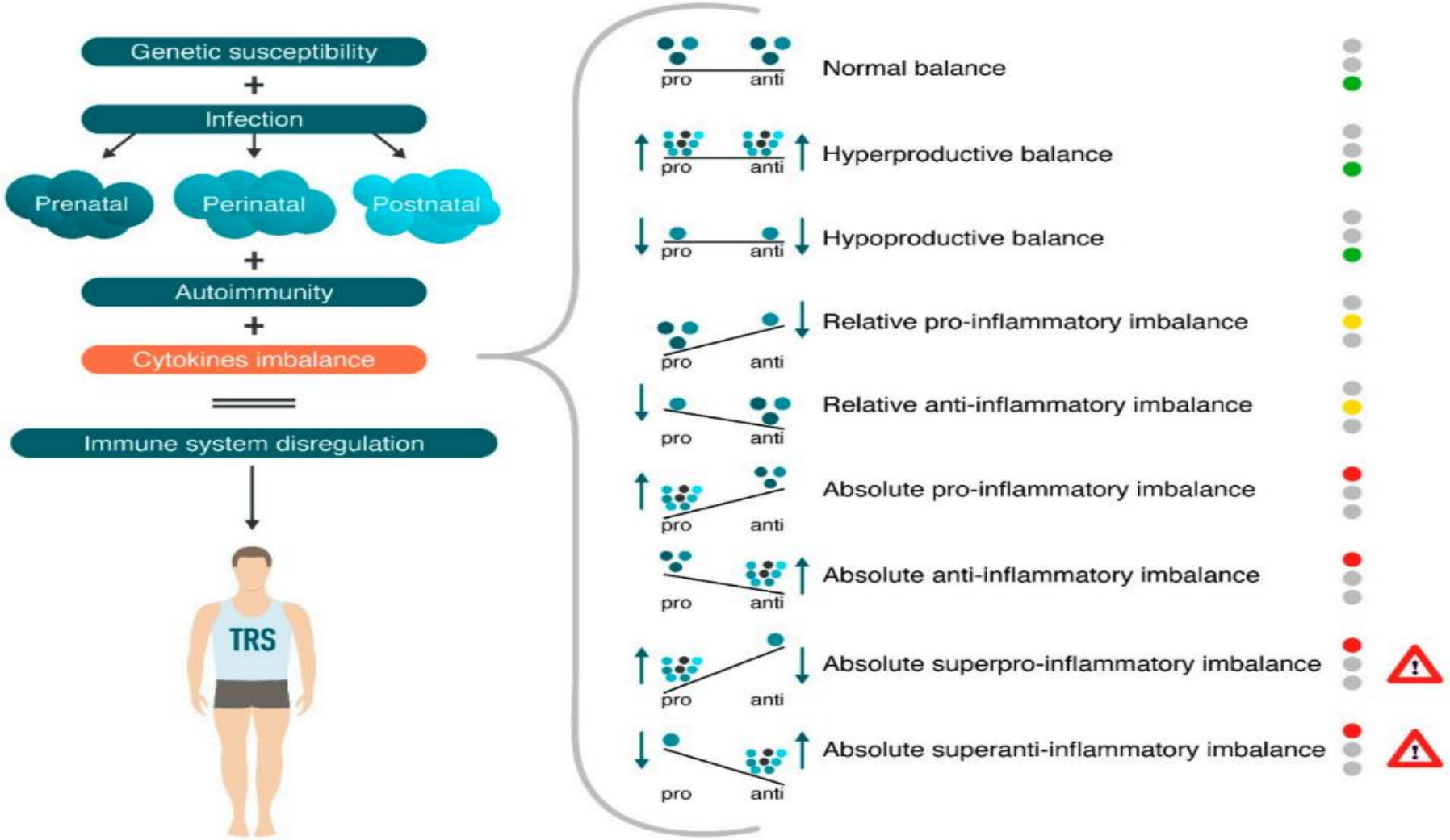
Pesquisas em Organoides

- Culturas de células células-tronco tridimensionais auto-organizadas.
  - diferenciação de tipos de células para modelar a organogênese in vitro.
  - recapitulam estágios de desenvolvimento e a estrutura organizacional do órgão
- Cérebro: organoides específicos da região e organoides cerebrais não específicos
  - Estudo de diferenças de expressão de genes ao longo do desenvolvimento em comparação com organoides neurotípicos
- Resultados principais:
  - defeitos na excitabilidade neuronal
  - sinalização de cálcio prejudicada
    - Ex perda heterozigótica de DGCR8/22q11.2: defeitos dos neurônios 22q11.2DS.
    - Aumento da expressão de DGCR8 recuperou a sinalização de cálcio nos neurônios (semelhante a tratamento com antipsicóticos)
- Potencial de organoides derivados do paciente: descoberta de alvos e triagem de abordagens terapêuticas in vitro.
  - Chen & Geshwind 2022

Balanço Pró-Anti inflamatório e Fase de doença

Note: APs—antipsychotics; DNA—deoxyribonucleic acid; Sch—schizophrenia.




Genetic susceptibility
+
Infection
Prenatal
Perinatal
Postnatal
+
Autoimmunity
+
Cytokines imbalance
Immune system disregulation
TRS
pro
anti
Normal balance
Hyperproductive balance
Hypoproductive balance
Relative pro-inflammatory imbalance
Relative anti-inflammatory imbalance
Absolute pro-inflammatory imbalance
Absolute anti-inflammatory imbalance
Absolute superpro-inflammatory imbalance
Absolute superanti-inflammatory imbalance

- Equilíbrio entre citocinas pró-inflamatórias e anti-inflamatórias determina o efeito de resposta neuroinflamatória em SZ.
- Perturbações do equilíbrio podem direcionar a resposta imune de defesa do paciente para cronicidade/resistência com neuroinflamação (pró-inflamatória) ou para a cicatrização (anti-inflamatória).
- Desequilíbrio inicial de citocinas pode ser benéfico para o paciente com Scz, iniciando a resposta neuroinflamatória
- Neuroinflamação crônica →desequilíbrio citocinas inflamatórias e anti-inflamatórias → alteração de neurotransmissores dopaminérgicos.
- A superprodução ou subprodução de medidadores pró-inflamatórios ou anti-inflamatórios (citocinas) podem ser deletérios para o paciente com Scz "não dopaminérgica"

Limitações de terapias imunoreguladoras

- Terapia anti citocinas pró-inflamatórias, paradoxalmente, pode levar a aumento da inflamação quando:

(1) Mutação de genes de citocinas

(2) Mutações somáticas e inflamação

(3) Citocinas pró-inflamatórias reduzidas devido a SNVs

Citocinas e reguladores pró-inflamatórios interconectados ao longo da evolução

Terapias isoladas de bloqueio de citocinas podem resultar em regulação positiva significativa de uma longa lista de genes e vias de sinalização, presumivelmente a "segunda onda de inflamação"

Segunda onda de inflamação pode ser o principal mecanismo das RA observadas em pacientes recebendo terapia Mab que bloqueia citocinas pró-inflamatórias

Bishop JR, Zhang L, Lizano P. Inflammation Subtypes and Translating Inflammation-Related Genetic Findings in Schizophrenia and Related Psychoses: A Perspective on Pathways for Treatment Stratification and Novel Therapies. Harv Rev Psychiatry. 2022 Jan-Feb 01;30(1):59-70.

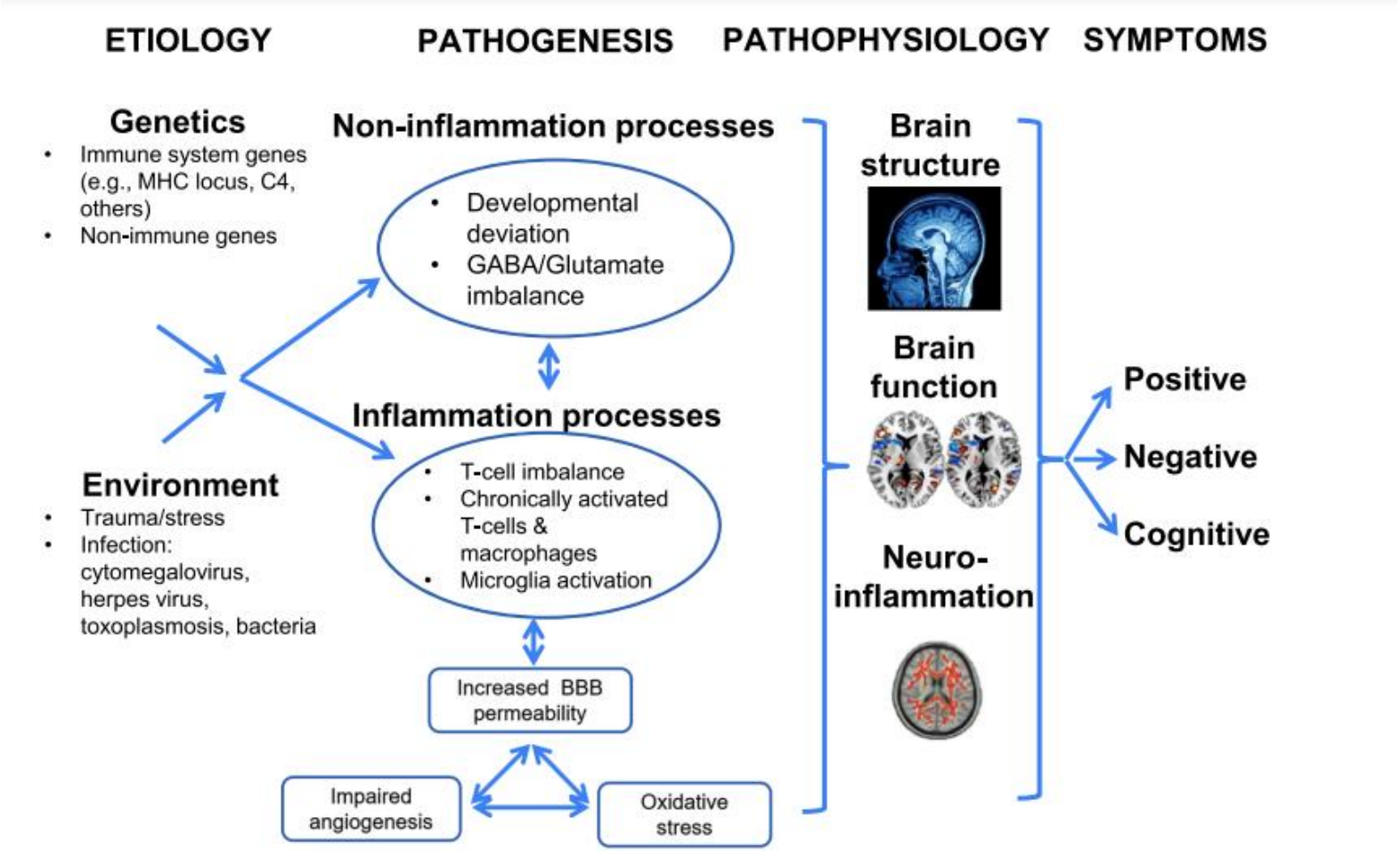


Figure 1. Conceptual model of immune dysregulation in psychosis. Converging evidence suggests that genetic and environmental factors increase peripheral inflammation that adversely affects the brain and clinical outcomes. BBB, blood-brain barrier; MHC, major histocompatibility complex.

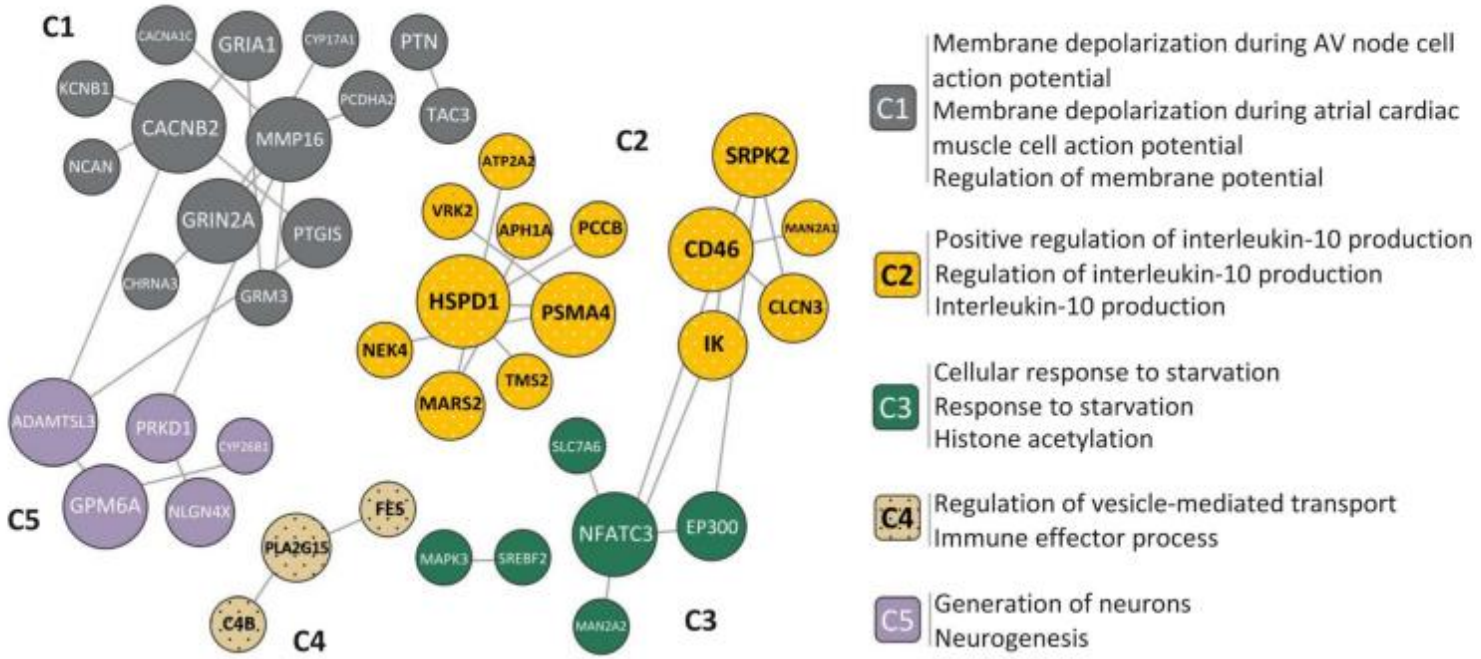


Figure 3. CNS-specific functional modules for druggable schizophrenia risk genes. The network is comprised of 42 out of 103 druggable genes assigned to one of five clusters (C1–C5) with significant membership. The network clustering was performed based on shared k-nearest-neighbors and community-finding algorithm.[87] Functional enrichment with genes annotated to Gene Ontology Biological Process (GO:BP) terms was examined across five clusters, with the top overrepresented GO:BP terms within each cluster listed on the right (the mapped gene list and full results of pathway enrichment are available in supplemental materials). C2 and C4 containing a total of 17 genes (with polka dots in figure) and 50 enriched terms had strong immune/inflammation implications associated with central nervous system function.

ISRCTN23256704 https://doi.org/10.1186/ISRCTN23256704

A trial to understand how immune function affects symptoms of psychosis

Submission date
28/06/2022

Registration date
13/07/2022

Last edited
23/08/2022

Recruitment status
Recruiting

Overall trial status
Ongoing

Condition category
Mental and Behavioural Disorders

✓ Prospectively registered

? Protocol not yet available

? SAP not yet available

– Results not yet expected

– Raw data not yet expected

✓ Record updated in last year

Resumo

- Drogas DA: 3ª geração, novas rotas, duração estendida 1-3-6 meses
- Associação com Antinflamatórios/Imunoreguladores/MAB
- Estudos fase II: ACH M1R, Complemento, Cca,
- Neuromodulação: ECT antinflamatório, tdcs, EMT CPFDLE
- Desafios: Fase de Doença – progressão – estabilização
- Potencial de prevenir dano - cura