Treatment of Psychiatric Disorders with Anti-Inflammatory Agents

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Robbins Textbook of Basic Pathology

- Table of content
  - Cell injury, cell death..(degenerative diseases)
  - Acute and chronic inflammation
  - Diseases of the immune system
  - Tissue repair : regeneration, healing, and fibrosis
  - Hemodynamic disorders, thrombosis, and shock (CVA)
  - Neoplasia
  - Environmental and nutritional diseases
  - Developmental disorders (genetic syndromes, congenital malformations)

So it is very likely that inflammation processes are pivotal in the pathological processes leading to psychiatric disorders

Agenda

- Evidence for immune abnormalities in depression and schizophrenia
- The evidence-based data on old-generation anti-inflammatory treatments for depression and schizophrenia
- Review of emerging studies with anti-cytokine agents
- Future directions

Evidence for Immune Abnormalities in Depression

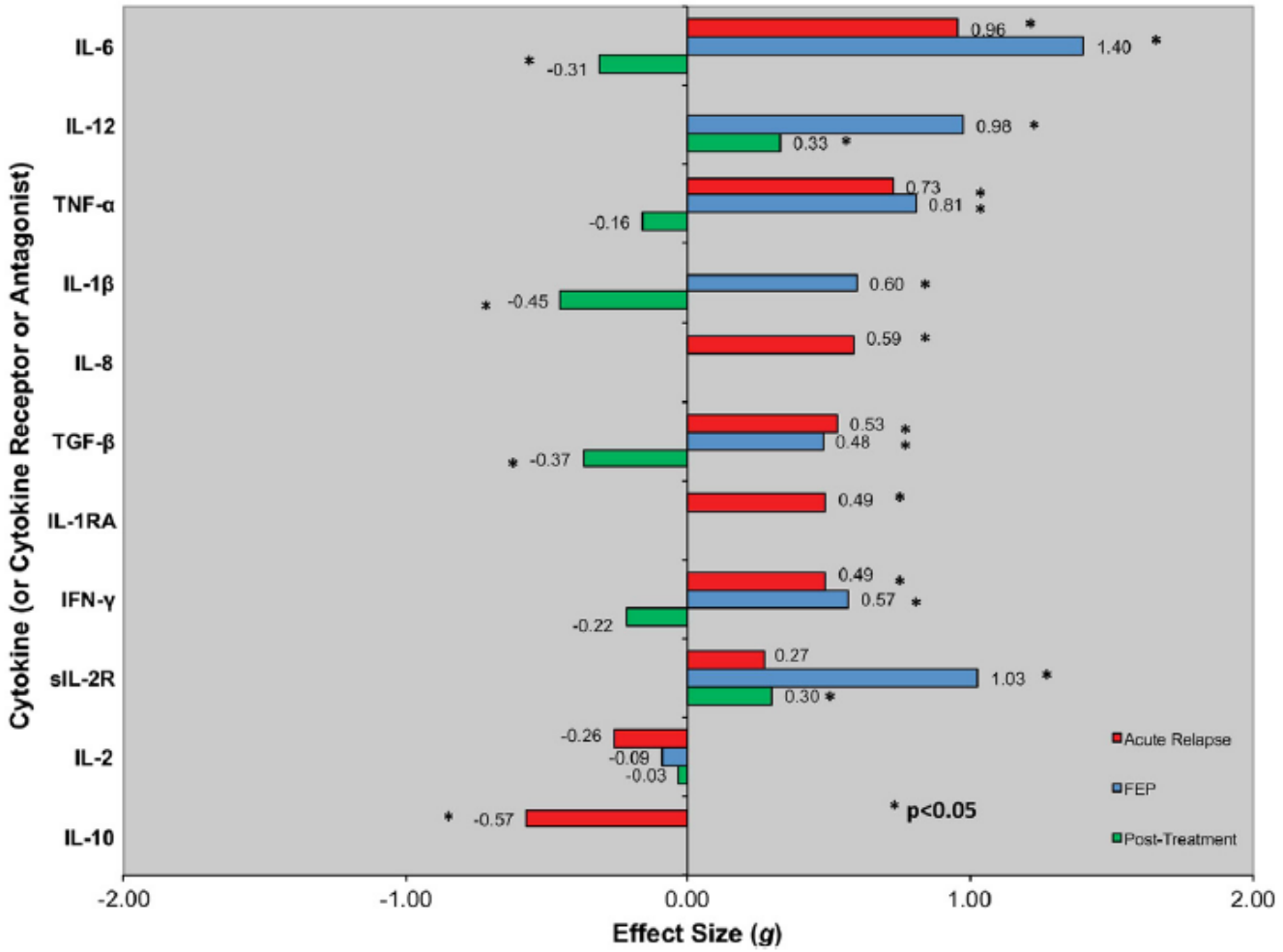
- Increased levels of pro-inflammatory cytokines in the blood and CSF-
  - **CRP**
  - **IL-6**
  - TNFα
  - IL-1 β
- Decrease in T regulatory cells (Tregs, Suppressor T cells) and levels of anti-inflammatory cytokines
  - IL-10
  - TGF-β

Inflammatory Markers and Resistance to Anti-Depressant Treatments

- Increased levels of inflammatory markers before antidepressant treatment predict poorer response to conventional antidepressant treatments
- Inflammatory factors (cytokines) decrease brain levels of serotonin and dopamine-
  - Increase expression of serotonin transporter
  - Reduce serotonin synthesis
  - Decrease dopamine release
- Induce astrocytic glutamate release that lead to decreased BDNF

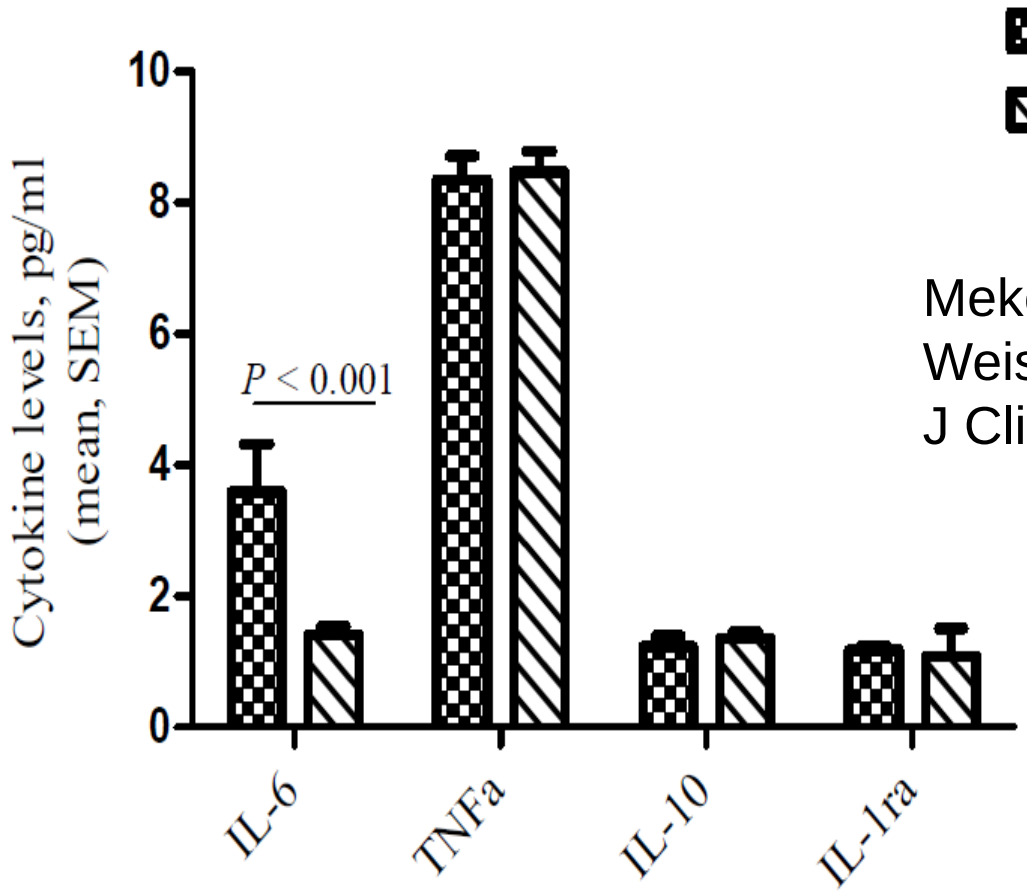
Miller AH Neuropsychophramacology Reviews 2016

Cytokine Levels in Schizophrenia



Girgis et al. biol psychiatry, 2014

High IL-6 Levels in 22q11.2 Deletion Syndrome with Psychotic Disorders



Mekori – Domachevsky, Taler, Weisman, Weizman, Gothelf
J Clin Psychiatry, 2017, in press

The Impact of Peripheral Inflammatory Response on the Brain

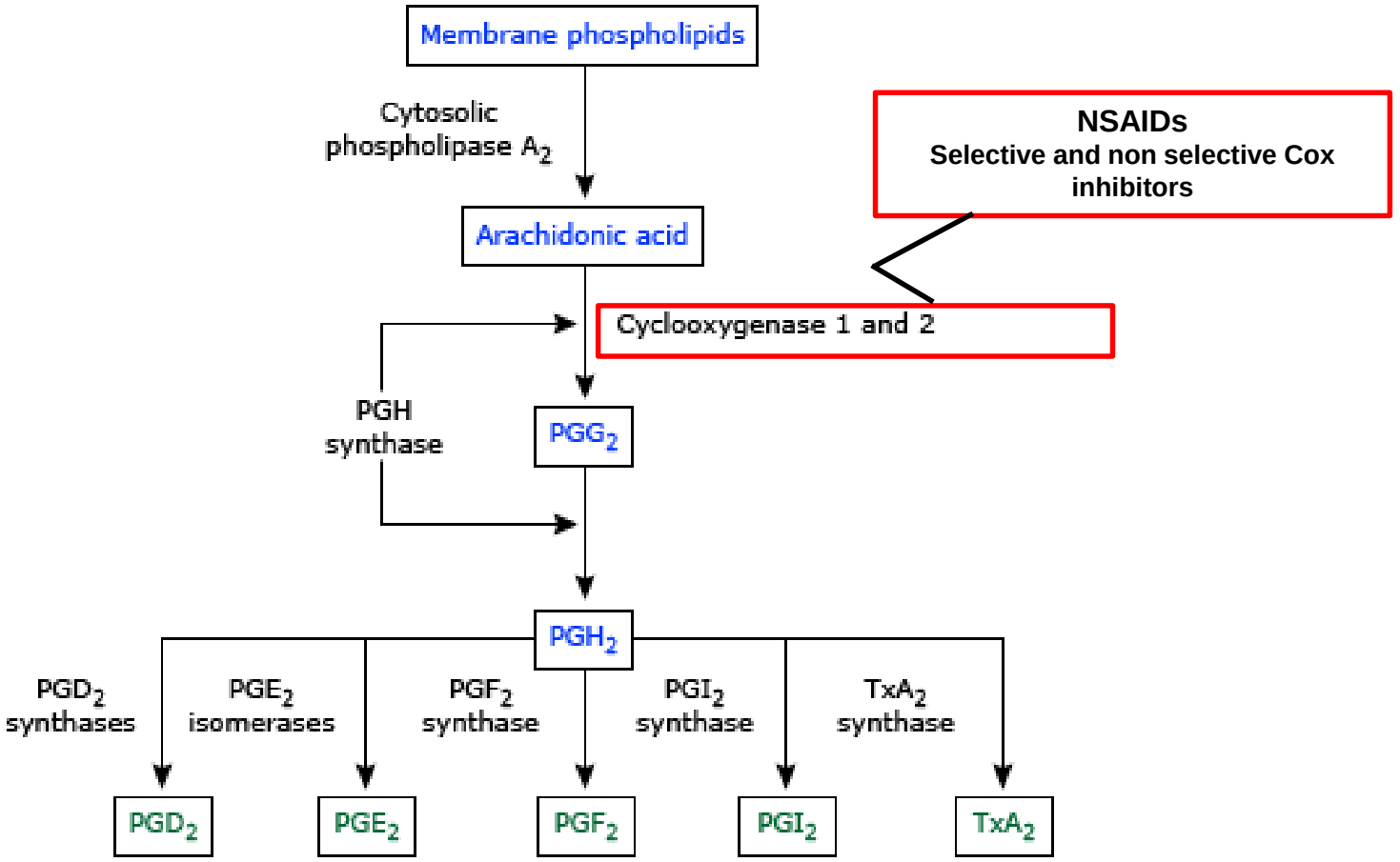
- Humoral route
  - Access of cytokines to the brain through leaky regions in the BBB
  - Through specific transport molecules
- Neural route
  - Activation of the vagus nerve by peripheral cytokines lead to induction of cytokine signals in the brain

Miller AH Neuropsychophramacology Reviews 2016

Anti-Inflammatory Drugs Studied in Schizophrenia and Depression

- NSAIDs
- Minocycline
- *N*-acetylcysteine
- Omega-3 fatty acids
- Anti-cytokine medications

NSAIDs & Specific Cyclooxygenase (COX) inhibitors



COX inhibitors

COX-1

- Expressed in most tissues
- Role in GI protection, vascular homeostasis, platelet aggregation, and kidney function

COX-2

Expressed in the brain, kidney and bones

- Upregulated during states of inflammation

NSAIDs

Non-selective COX1/2 inhibitors

Aspirin
Ibuprofen (Advil)
Diclofenac (Voltaren)
naproxen (Naxyn)

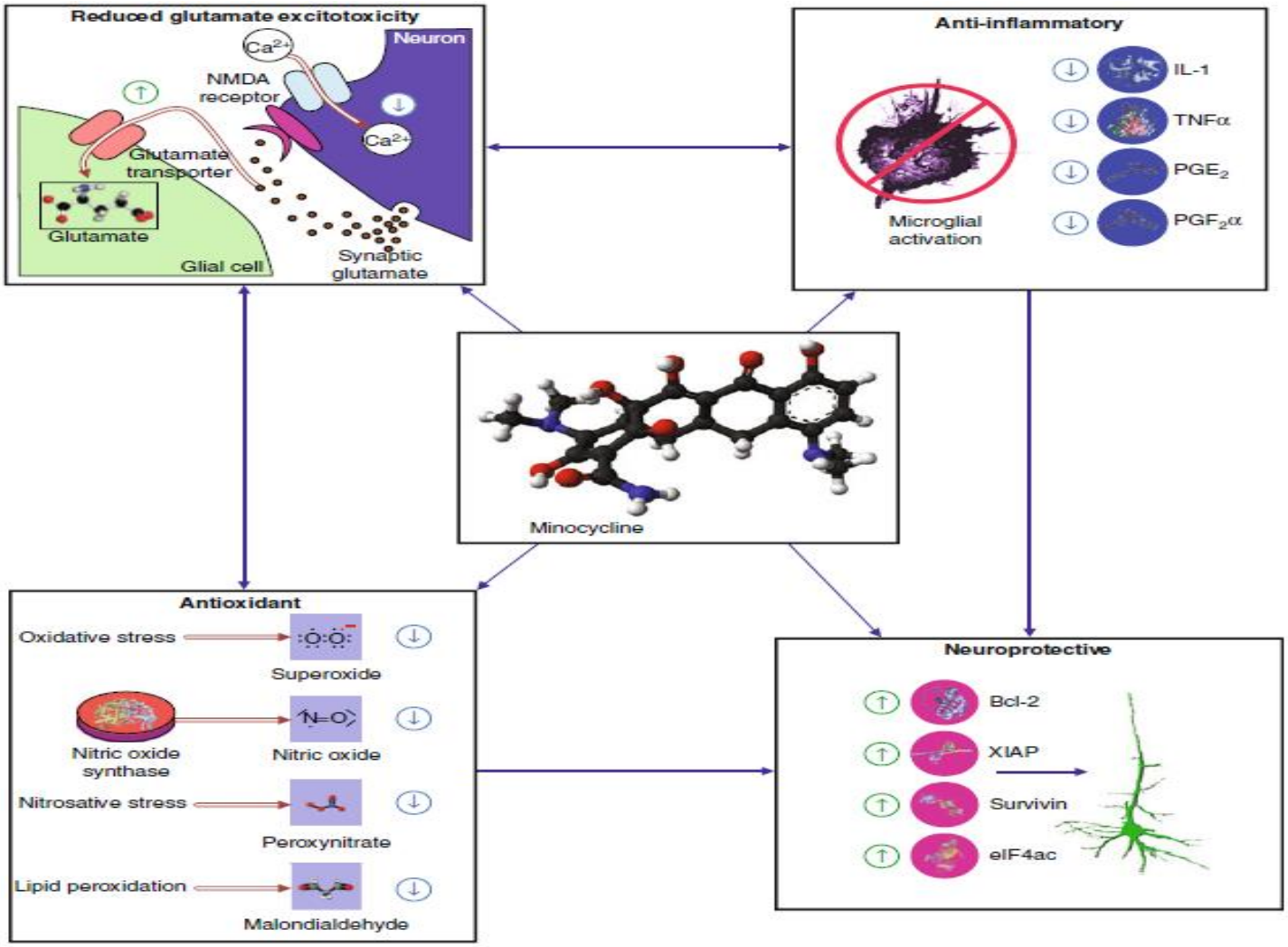
Selective COX2 inhibitors

Celecoxib (Celebra)
Etoricoxib (Arcoxia)

Minocyclin

- **Broad spectrum antibiotic**
  - semisynthetic derivative of tetracycline. Acts by inhibiting protein synthesis (inhibiting bacterial ribosome subunit 30S)
- **Medical indications**
  - Infections, acne, inflammatory diseases (autoimmune – RA, sarcoidosis)
- **Trials in neuropsychiatric disorders**
  - Schizophrenia
  - Affective disorders
  - OCD
  - Addiction
  - Dementia, Parkinson, Huntington

Minocyclin: CNS Effects



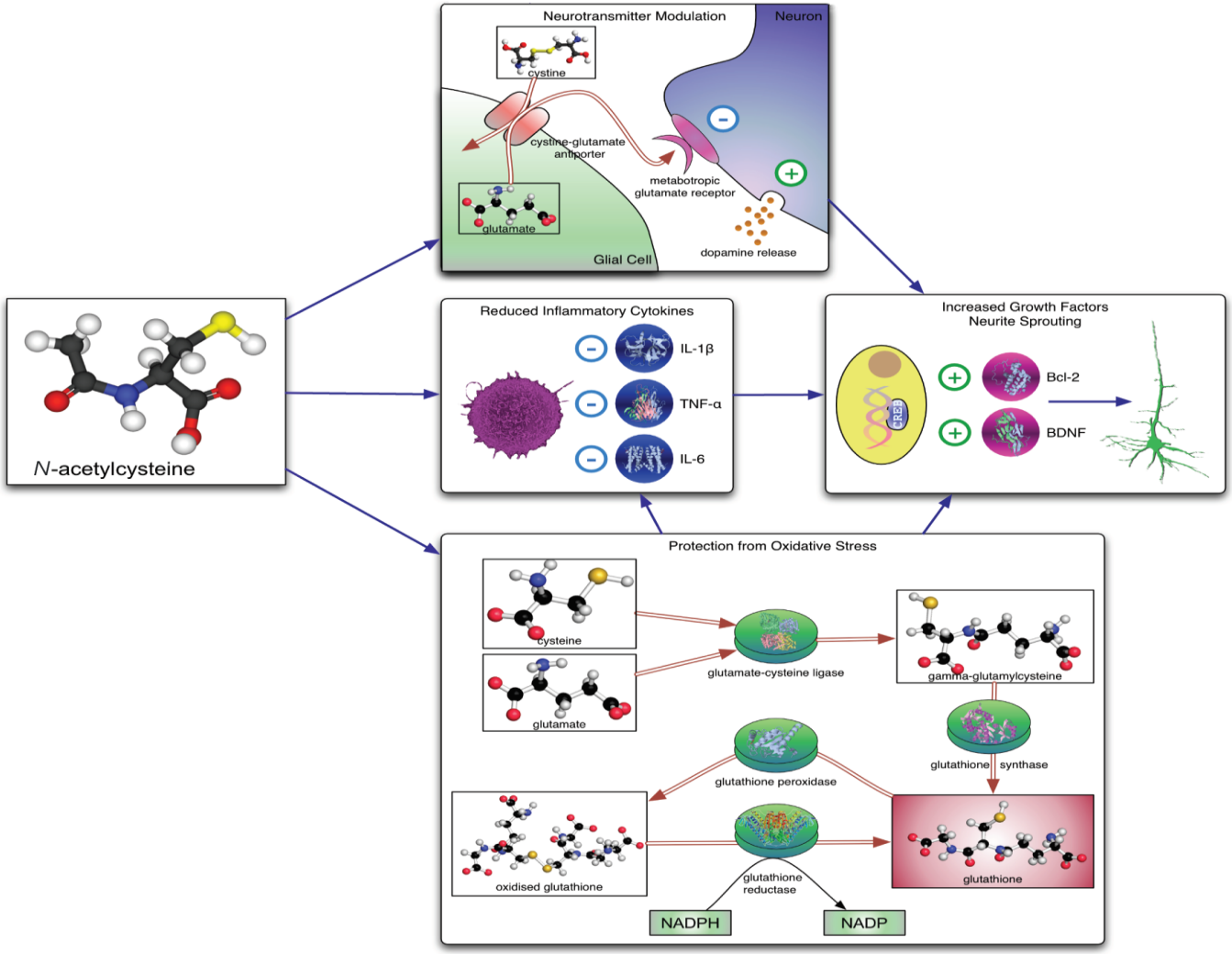
N-acetylcysteine

- **Medical indications**
  - Acetaminophen (Acamol) overdose
  - Mucolytic (COPD, CF, atelectasis)
- **Trials in psychiatric disorders**
  - Unipolar and bipolar depression
  - Schizophrenia
  - Trichotillomania, nail biting, skin picking
  - OCD
  - Nonsuicidal self injury (NSSI)
  - Addiction (marijuana, cocaine, nicotine, methamphetamine, pathologic gambling)
  - Cognitive impairment and Alzheimer's disease

N-acetylcysteine

- **Mechanisms of action**
  - hepatoprotective agent by restoring hepatic glutathione
  - Cleavage of disulfide bonds in the mucoproteins thus lowering mucous viscosity
- **Common side effects with oral administration**
  - Gastrointestinal: GI symptoms, nausea, vomiting

N-acetylcysteine CNS Effects



Anti-Inflammatory Agents for Depression:
studies with post treatment scores only

reference	Anti-inflammatory used	Add on (vs. placebo)	N of patients analyzed	SMD (95%CI)
Berk et al., 2008	NAC	TAU	75	0.76
Jafari et al., 2015	Celecoxib	antibiotic	40	2.02
Majid et al., 2015	Celecoxib	SSRI	23	0.66
Müller et al., 2006	Celecoxib	NARI	18	0.52
Nery et al., 2008	Celecoxib	TAU	28	0.02
Saroukhani et al., 2013	Aspirin	Lithium	30	0.26
Total				**0.71(0.17-1.24)**

- Duration of treatment: 6-24 weeks
- Celecoxib 400 mg/day; Aspirin 1000 mg/day, NAC 2000 mg/day

Husain et al., Anti-inflammatory treatments for mood disorders: Systematic review and meta-analysis Journal of Psychopharmacology, 2017

Anti-Inflammatory Agents for depresssion-
studies with pre and post depressive symptom scores

reference	Anti-inflammatory used	Add on (vs. placebo)	N of patients analyzed	SMD (95%CI)
Abbasi et al.,2012	Celecoxib	SSRI	37	0.92
Akhondzadeh et al., 2009	Celecoxib	SSRI	37	0.73
Emadi- ouchak et al., 2016	Minocycline	Monotherapy	46	1.06
Magalhães et al., 2011	NAC	TAU	14	0.18
Raison et al., 2012	Infliximab	Monotherapy	60	-0.28
Total			**194**	**0.52 (0.05-1.10)**

- Duration of treatment: 6-24 weeks

Anti-Inflammatory Agents for Bipolar-mania scores

reference	Anti-inflammatory used	Add on to (vs. placebo)	N of patients analyzed	SMD (95%CI)
Arabzadeh et al., 2015	Celecoxib	Valproate	46	1.22
Kargar et al., 2015	Celecoxib	ECT	35	0.40
Magalhães et al., 2013	NAC	TAU	13	0.37
Total			**94**	**0.72 (0.13-1.31)**

- Duration of treatment: 6-24 weeks

Effect Size in Anti-inflammatory vs. Conventional Treatments

Treatment	Indication	Effect Size
Anti-inflammatory agents	MDD	0.52-0.71
SSRIs [1]	MDD	0.34 0.61 (severe depression)
Augmentation with atypical antipsychotic [2]	MDD	Aripiprazole- 0.35 Quetiapine- 0.45 Risperidone- 0.48
Anti-inflammatory agents	Mania	0.72
Mood stabilizers [3]	Mania	Lithium- 0.8

[1] Thase et al. Assessing the 'true' effect of active antidepressant therapy v. placebo in major depressive disorder: use of a mixture model, The British Journal of Psychiatry, 2011

[2] Spielmans et al., Adjunctive atypical antipsychotic treatment for major depressive disorder: A meta-analysis of depression, quality of life, and safety outcomes, PLOS Medicine, 2013

[3] Popvic et al. number needed to treat analyses of drugs used for maintenance treatment of bipolat disorder, Psychopharmacology, 2010

Omega-3 Polyunsaturated Fatty Acids: Medical Indications

- protective factor for cardiac disease and metabolic syndrome
- Decreases levels of triglycerides and LDL cholesterol and increases HDL cholesterol
- Decreases blood pressure
- Protects against atherosclerotic plaques
- Treatment for autoimmune disease- lupus, RA, ulcerative colitis, Crohn's, psoriasis, DM type I

Omega3: Anti-inflammatory Mechanisms

- HUFAs are important components of neuronal cell membrane, especially of dendritic and synaptic membranes.
- Inhibits production of endotoxin-stimulated production of cytokines
- Decrease activity of inflammatory cells (monocytes, macrophages and neutrophils)
  - Decrease chemotaxis
  - Decreased expression of adhesion molecules
- Decrease production of arachidonic acid derivatives like prostaglandins

Omega-3 Fatty Acids

- Other mechanisms of action
  - anti-oxidative
  - increase serotonin and dopamine receptor expression
- No major side effect
  - fishy taste, stomach upset, loose stools, nausea

Omega-3 Trials in psychiatric disorders

הפרעה	מספר מחקרים	יעילות
Depression	20 RCTs (mild and moderate depression) 6 meta analyses	
Schizophrenia	13 RCTs (11 add on; 2 monotherapy but AP was added during the trials) 4 meta analyses	
Bipolar disorder	7 RCTs (1 monotherapy;6 augmentation) 4 meta analyses	Improvement of bipolar depressive symptoms but not manic symptoms
ADHD	13 RCTs 4 meta analyses	Small to modest effect sizes

Bozzatello et al,. Journal of Clinical Medicine, 2016

Omega-3 Trials in psychiatric disorders

הפרעה	מספר מחקרים	יעילות
ASD	5 RCTs; 1 case study; 1 open label study; 1 systematic review 1 meta analysis	2 RCTs significant improvement in lethargy symptoms 1 RCT significant improvement in daily-living 2 RCTs significant worening of both externalizing behavior and social deficits
OCD	1 RCTs (augmentation)	No significant improvement
Borderline personality disorder	3 RCTs	Efficacy on aggressive behaviors, depressive symptoms, para-suicidal behavior, stress reactivity, impulsive behavior
Substance dependence	2 RCTs	Significant reduction in anxiety
Anorexia nervosa	2 studies	small study (7 patients)- improvement in sleep, mood, dry skin and constipation. Another small RCT (10 patients) -no efficacy on weight gain, anxiety or OC symptoms

Omega-3 for MDD Compared to Placebo

N studies	N patients	Effect Size	CI	Clinical Significance
25	1438	0.30	0.10-0.50	2.1 point decrease in HDRS = clinically insignificant!!!

Appleton et al Omega-3 fatty acids for depression in adults. an abridged Cochrane review. BMJ Open 2016

Inflammation Markers as Predictors for Response to Omega3 in MDD

- 8 weeks double-blind 3-arms trials-
  - EPA-enriched (n=60, 530mg EPA / 130 mg DHA)
  - DHA-enriched (n=58, 225mg DHA / 45mg EPA)
  - Placebo (n=52)
- Inflammation markers measured at baseline-
  - hs-CRP
  - IL-6
  - IL-1ra
  - Leptin
  - Adiponectin (anti-inflammatory factor)

Rapaport Mol Psychiatry 2016:71-79

Inflammation Markers as Predictors for Response to Omega3 in MDD

- High inflammatory status hs-CRP>3
  - IL-6>1.9
  - IL-1ra>500
  - Leptin
    - males>70
    - Females>250
  - Adiponectin (anti-inflammatory factor)<70
- High inflammatory status ranged from 24%- hs-CRP to 43%- leptin
- Double figures for obese individuals

Rapaport Mol Psychiatry 2016:71-79

Inflammation Markers as Predictors for Response to Omega3 in MDD

- No differences among 3 groups (EPA, DHA and placebo)
- Subjects with 1 or more high biomarkers at baseline of inflammation improved more on EPA than placebo (ES=0.39) or DHA (ES=0.60)
- Combinations of several high inflammatory factors at baseline (e.g., high hsCRP and IL-1ra and low adiponectin) was associated with stronger response

Rapaport Mol Psychiatry 2016:71-79

Celecoxib as Adjunctive Treatment for Schizophrenia

Type of outcome	ES (95% CI)
Total psychopathology	-0.22 (-0.54- 0.10)
Positive symptoms score	-0.23 (-0.56-0.10)
Negative symptoms score	-0.12 (-0.37-0.13)
General psychopathology score	-0.13 (-0.36- 0.11)

- None of the effect sizes was significant
- **8 RCTs** included (**316 patients** on celecoxib 400 mg/day)
- Duration of treatment: 5-12 weeks
- Add on to (vs. placebo): risperidone (n=5); clozapine (n=1); amisulpride (n=1); risperidone/olanzapine (n=1)

Zheng et al,. Adjunctive celecoxib for schizophrenia: A meta-analysis of randomized, double-blind, placebo-controlled trials, Journal of Psychiatric Research, 2017

Celecoxib as Adjunctive Treatment of First Episode Schizophrenia

Type of outcome	ES (95% CI)
Total psychopathology	-0.47 (-0.81-0.14)*
Positive symptoms score	-0.50 (-0.79-0.20)*
Negative symptoms score	-0.32 (-0.66-0.02)
General psychopathology score	-0.35 (-0.65-0.06)*

- **3 RCTs** included (**96 patients** on celecoxib 400 mg/day)
- Duration of treatment: 5-8 weeks
- Add on to (vs. placebo): risperidone (n=2); amisulpride (n=1)

Zheng et al,. Adjunctive celecoxib for schizophrenia: A meta-analysis of randomized, double-blind, placebo-controlled trials, Journal of Psychiatric Research, 2017

Minocyclin as Adjunctive Treatment for Schizophrenia

	SMD (95%CI)
Total psychopathology *	0.64 (0.27-1.02)
Positive symptom score*	0.22 (0.03-0.41)
Negative symptom score*	0.69 (0.40-0.98)
General symptom score*	0.45 (0.09-0.82)

- **8 RCTs** included (**286 patients** on minocycline 171.9±31.2 mg/day)
- Duration of treatment: 8-48 weeks
- Add on to (vs. placebo): risperidone (n=5); clozapine (n=1); other antipsychotics (n=2); no report (n=1)
- Scores were strongly influenced by: Chinese participants, treatment with risperidone, and older participants (>32 years old)

Xiang et al. European Neuropsychopharmacology, 2017

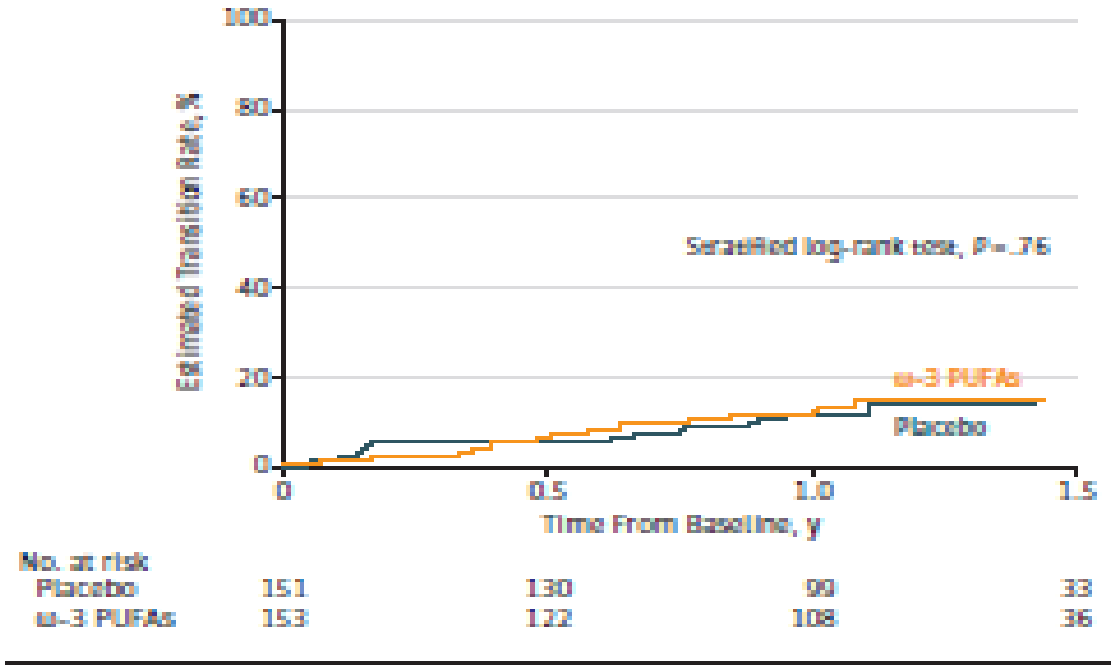
Omega-3 as Adjunctive Treatment for Schizophrenia

- Ten studies included in the meta-analysis
- **First-episode schizophrenia-** omega-3 decreased nonpsychotic symptoms, lowered the required antipsychotic medication dosages
- **Stable chronic schizophrenia**- no positive effect

Chen AT et al. A meta-analysis of placebo-controlled trials of omega-3 fatty acid augmentation in schizophrenia: Possible stage-specific effects. Ann Clin Psychiatry 2015; 27: 289-96

Omega- 3 in Prodrome

Figure 2. Survival Curves of the Rate of Transition to Psychosis in the ω-3 Polyunsaturated Fatty Acid (ω-3 PUFA) and Placebo Groups



- A multicenter RCT
- (n= 304)
- Long term follow up
- Use of omega-3 is not effective under conditions in which evidence-based and good-quality psychosocial treatment are available.

Transition rates:
Omega-3: 6.7%
Placebo: 5.1%

McGorry et al., JAMA Psychiatry 2017

Potential Bias in the Results of the Studies Presented

- The majority of studies were small
- Overall number of participants studied was low
- Results influenced by a few large trials
- inadequate reporting of withdrawals and drop-outs and indadequate control of confounders
- Effect size estimates are also imprecise evidenced by funnel plot asymmetry and sensitivity analyses

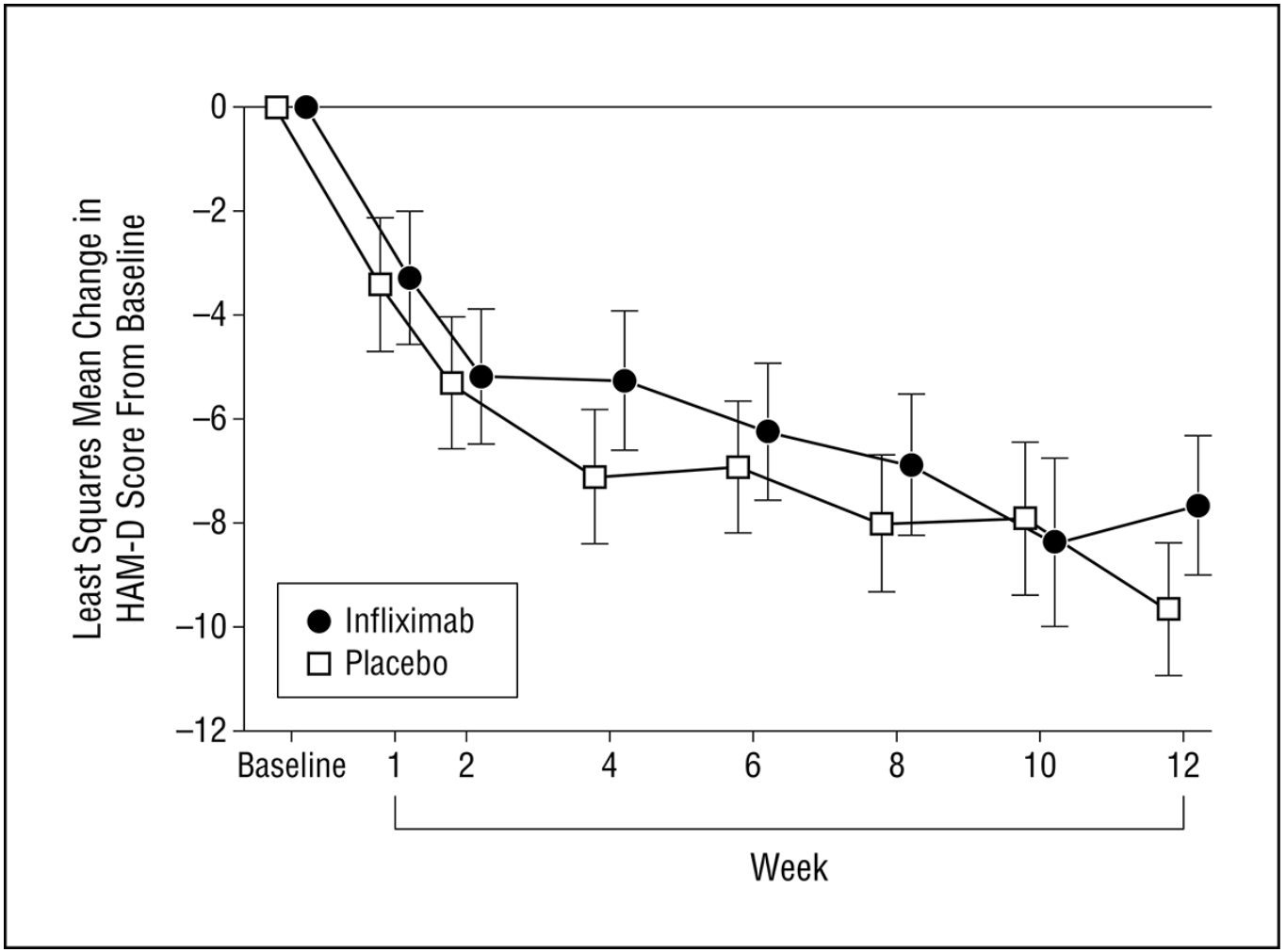
Anti-Cytokine Treatments

TNF-alpha Antagonist (Infliximab) for Resistant Depression

- 60 outpatients with medium severity resistant depression (UP or BP) age 25 to 60
- Inclusion of patients with hs-CRP>2mg/L
- 12 weeks double-blind placebo controlled study
- Infusion of infliximab (Remicade) 5mg/kg or placebo at weeks 0, 2, 6
- 90% completed the study (25/30 infliximab 29/30 placebo)
- None of the side effects was more common in patients receiving infliximab compared to placebo

Raison JAMA Psychiatry 2013; 70:31-41

TNF-alpha Antagonist (Infliximab) for Resistant Depression



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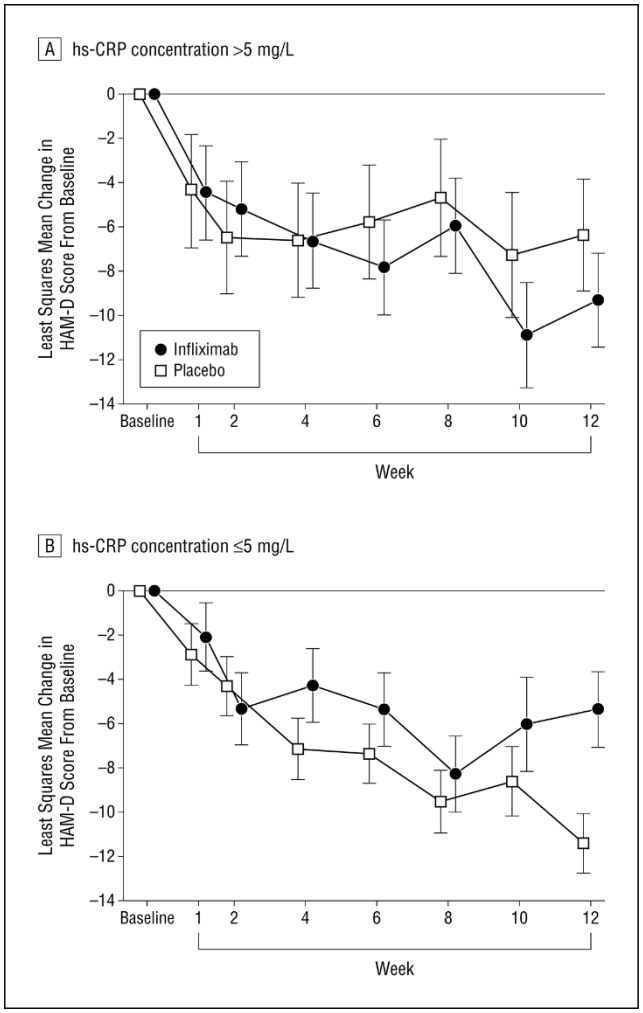
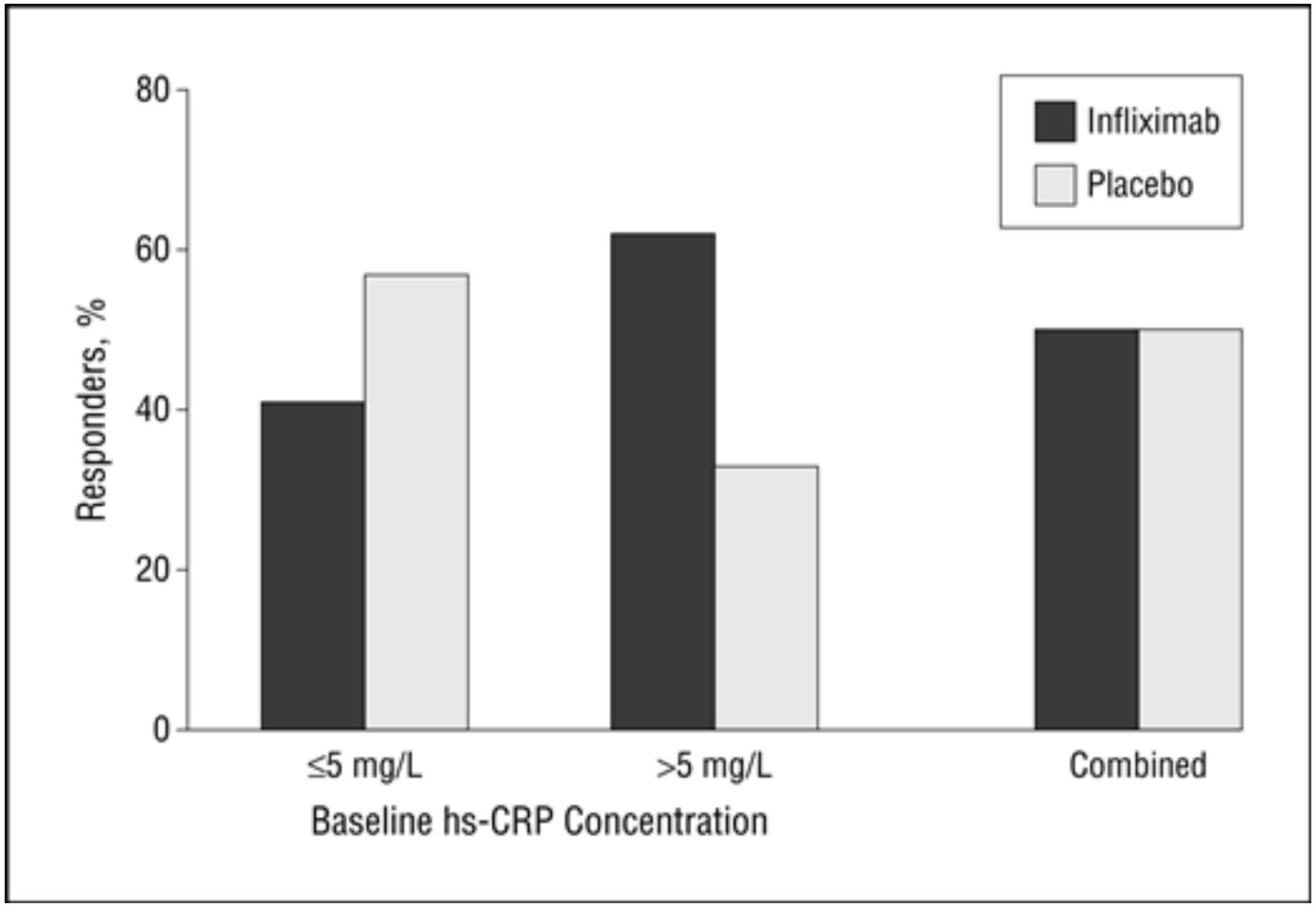
TNF-alpha Antagonist (Infliximab) for Resistant Depression



Raison JAMA Psychiatry 2013; 70:31-41

Remission Rates



Raison JAMA Psychiatry 2013; 70:31-41

An RCT of Toclizumab for Residual Symptoms in Schizophrenia

- 36 individuals clinically stable, moderately symptomatic (PANSS>60) with schizophrenia
- 3 months study- monthly infusions of toclizumab (IL-6 Receptor Ab) or placebo (normal saline)
- No effects on symptoms or cognition
- "One potential explanation is the lack of capacity of this agent to penetrate the CNS"
- "Additional trials of medications aimed at targeting cytokine overactivity that act directly on brain function and/or treatment in early stage psychosis populations are needed"

Girgis et al Neuropsychopharmacology 2017 in press

Conclusions

- Nonspecific treatments with some anti-inflammatory activity (e.g., NSAID, Minocyclin and NSAIDs) have statistically significant effect on depressive and schizophrenia symptoms (minocycline- negative symptoms, celecoxib and omega3- first episode)
- Yet, the clinical significance of the effects are between negligible (omega3) or yet to be proven in large scale (phase III) studies
- To date, there are only a few studies on the effect of anti-cytokines agents in depression and schizophrenia

Recommended Design for Future Anti-Inflammatory Studies in Psychiatry

- Should try anti-cytokine (‘biological’) treatments
  - Potent anti-inflammatory activity
  - Specificity
  - No off-target effects
- Anti-TNF Abs → infliximab (remicade), humera
- Anti-IL-6 Abs → toclizumab, siltuximab
- Anti-IL-1β Abs → canakinumab

Miller AH Neuropsychophramacology Reviews 2016

Recommended Design for Future Anti-Inflammatory Studies in Psychiatry

- Comparing psychiatric patient population with high vs. low inflammation markers
- Focus on early stages of the disease (especially for psychotic disorders)
- Studying specific immunological agents that are able to penetrate the blood-CNS barrier (such as the medications in multiple sclerosis)

Conclusions

- Should take an RDoC approach and study systems that are affected by inflammation-
  - Reward system
  - Negative valence (anxiety)
  - Psychomotor retardation
  - Cognitive functioning
  - Sleep
  - Negative symptoms of schizophrenia