Section of

Perinatal Psychiatry

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Viewpoint

Viewpoint | European COVID-19 exit strategy for people with severe mental disorders: Too little, but not yet too late

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Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors

Mario Gennaro Mazza[a,b,*], Rebecca De Lorenzo[b,c], Caterina Conte[b,c], Sara Poletti[a,b], Benedetta Vai[a,b], Irene Bollettini[a,b], Elisa Maria Teresa Melloni[a,b], Roberto Furlan[b,d], Fabio Ciceri[b,c], Patrizia Rovere-Querini[b,c], and the COVID-19 BioB Outpatient Clinic Study group, Francesco Benedetti[a,b]

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ABSTRACT

Infection-triggered perturbation of the immune system could induce psychopathology, and psychiatric sequelae were observed after previous coronavirus outbreaks. The spreading of the Severe Acute Respiratory Syndrome Coronavirus (COVID-19) pandemic could be associated with psychiatric implications. We investigated the psychopathological impact of COVID-19 in survivors, also considering the effect of clinical and inflammatory predictors.

We screened for psychiatric symptoms 402 adults surviving COVID-19 (265 male, mean age 58), at one month follow-up after hospital treatment. A clinical interview and a battery of self-report questionnaires were used to investigate post-traumatic stress disorder (PTSD), depression, anxiety, insomnia, and obsessive-compulsive (OC) symptomatology. We collected sociodemographic information, clinical data, baseline inflammatory markers and follow-up oxygen saturation levels.

A significant proportion of patients self-rated in the psychopathological range: 28% for PTSD, 31% for depression, 42% for anxiety, 20% for OC symptoms, and 40% for insomnia. Overall, 56% scored in the pathological range in at least one clinical di[illegible] of baseline inflammatory markers, fem[illegible] for both anxiety and depression. Patients with a positive previous psy[illegible] showed increased scores on most psychopathological measures, with similar baseline inflammation. Baseline systemic immune-inflammation index (SII), which reflects the immune response and systemic inflammation based on peripheral lymphocyte, neutrophil, and platelet counts, positively associated with scores of depression and anxiety at follow-up.

[illegible] depression, and anxiety, are all high-burden non-communicable conditions [illegible] of life lived with disability. [illegible] mental health, the current insights on inflammation in psychiatry, and the present observation of worse inflammation leading to worse depression, we recommend to assess psychopathology of COVID-19 survivors and to deepen research on inflammatory biomarkers, in order to diagnose and treat emergent psychiatric conditions.

Everything you've always wanted to know about mental health, its effects on the brain and the body, and the science behind it

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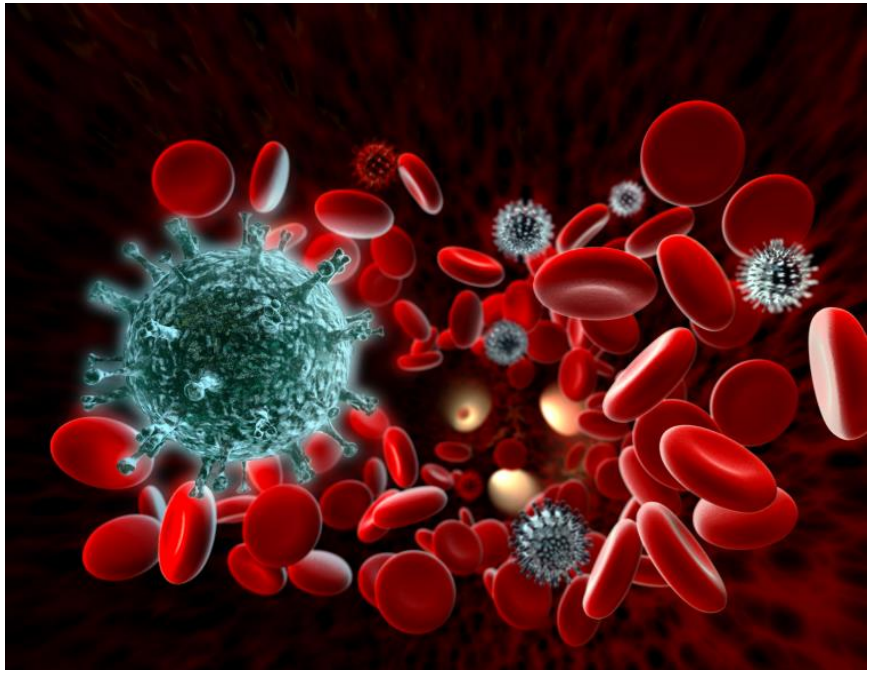
The year of immunopsychiatry: A special issue that foresaw the future

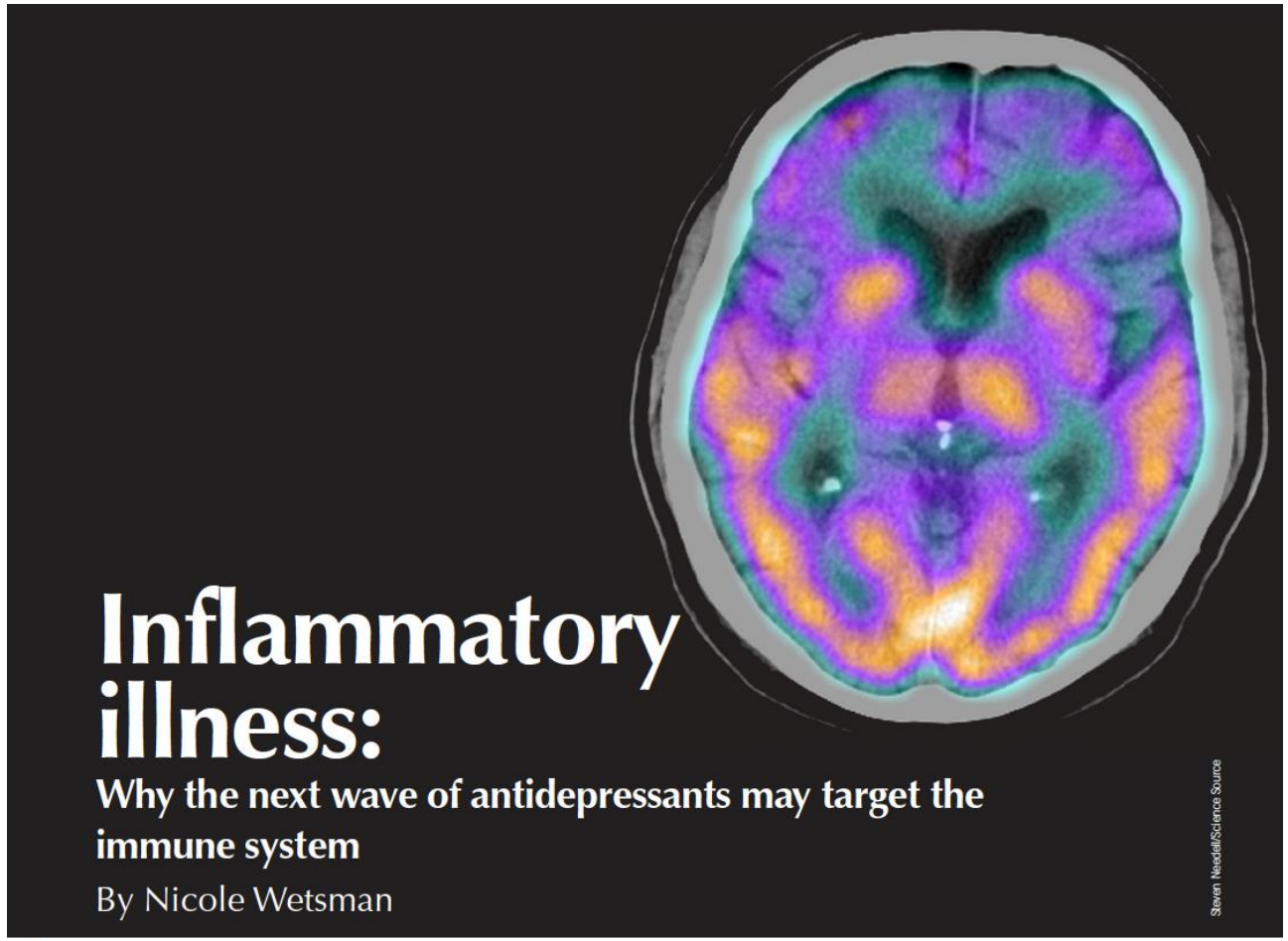
One year ago, *Psychoneuroendocrinology* launched this Special Issue on Immunopsychiatry, which I have had the pleasure to guest-edit, with a specific focus on understanding 'how relevant is the interface between the immune and neuroendocrine system for psychiatric disorders'.

I have already discussed extensively the notion that the recent introduction of the term 'immunopsychiatry' to describe this area of research defines a different, although obviously overlapping, theoretical framework compared with 'psychoneuroimmunology' (Pariante, 2018, 2015): it represents a hierarchical shift, from using psychological interventions to affect immunity (and hence health and disease) to targeting the immune system in order to have therapeutic benefits for both behaviour and emotions (and hence mental health and mental disorders).

babies in the perinatal period (Osborne et al., 2018; Rackers et al., 2018), children and adolescents (Lipschutz et al., 2018; Michels et al., 2018; Yirmiya et al., 2018), people with obesity or diabetes (Delgado et al., 2018; Herder et al., 2018), as well as patients with mental disorders whose immune correlates have been less studied so far, such as panic disorder (Petrowski et al., 2018), autism (Basheer et al., 2018; Marazziti et al., 2018), drug addiction (Kuo et al., 2018), bipolar disorder (Ozpercin et al., 2018; Queissner et al., 2018), and patients with late-onset (Rozing et al., 2019) or treatment-resistant (Bekhbat et al., 2018; Haroon et al., 2018) or anxious (Menke et al., 2018) or anhedonic (Jha et al., 2018) depression.

The animal studies confirm that basic science can give us important, clinically- and translationally-relevant information. For example, zeb-





Inflammatory illness:

Why the next wave of antidepressants may target the immune system

By Nicole Wetsman

Steven Needell/Science Source

In the winter of 1883, a psychiatric assistant named Julius Wagner-Jauregg was working in an Austrian asylum when he witnessed something curious. While making his rounds, Wagner-Jauregg encountered a woman with psychotic delusions who had caught a skin infection, which caused a high fever. But once her temperature resolved, she became coherent, and her symptoms of psychosis disappeared. Wagner-Jauregg spent the next decades of his career attempting to replicate that observation: he exposed people with mental illness to different types of infection to induce fever. But he had relatively little success until 1917,

But a year after Wagner-Jauregg received his Nobel Prize, a discovery occurred in London that would ultimately cause malariotherapy to fall out of style: Alexander Fleming struck upon penicillin, and within three decades, it became the go-to treatment for syphilis. Malariotherapy became a historical footnote, and Wagner-Jauregg's psychiatric legacy was quickly overshadowed by the dubious ethics of his experiments and his support of Nazism and eugenics.

Wagner-Jauregg had no clear sense of why malariotherapy worked—and he said as much in his Nobel Prize acceptance speech.

anti-inflammatory component that may have brought into balance an out-of-whack inflammatory system that could have been contributing to his patients' mental illness.

These insights didn't just function to explain the possible mechanism of the century-old malariotherapy protocol—which would never fly in modern-day psychiatric care, for a range of reasons—but paved the way for a new line of inquiry in psychiatry. The underlying principle that the immune system is important in mental illness is regaining momentum, particularly in depression. A study published in July looking at blood samples from 113 patients with severe

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Page 1 of 9. doi: 10.1192/bjp.2018.66

Treatment-resistant depression and peripheral C-reactive protein

Samuel R. Chamberlain, Jonathan Cavanagh, Peter de Boer, Valeria Mondelli, Declan N.C. Jones, Wayne C. Drevets, Philip J. Cowen, Neil A. Harrison, Linda Pointon, Carmine M. Pariante* and Edward T. Bullmore*†

Background

C-reactive protein (CRP) is a candidate biomarker for major depressive disorder (MDD), but it is unclear how peripheral CRP levels relate to the heterogeneous clinical phenotypes of the disorder.

Aim

To explore CRP in MDD and its phenotypic associations.

Method

We recruited 102 treatment-resistant patients with MDD currently experiencing depression, 48 treatment-responsive patients with MDD not currently experiencing depression, 48 patients with depression who were not receiving medication and 54 healthy volunteers. High-sensitivity CRP in peripheral venous blood, body mass index (BMI) and questionnaire assessments of depression, anxiety and childhood trauma were measured. Group differences in CRP were estimated, and partial least squares (PLS) analysis explored the relationships between CRP and specific clinical phenotypes.

Results

Compared with healthy volunteers, BMI-corrected CRP was significantly elevated in the treatment-resistant group ($P = 0.007$; Cohen's $d = 0.47$); but not significantly so in the treatment-responsive ($d = 0.29$) and untreated ($d = 0.18$) groups. PLS yielded an optimal two-factor solution that accounted for 34.7% of variation in clinical measures and for 36.0% of variation in CRP. Clinical phenotypes most strongly associated with CRP and heavily weighted on the first PLS component were vegetative depressive symptoms, BMI, state anxiety and feeling unloved as a child or wishing for a different childhood.

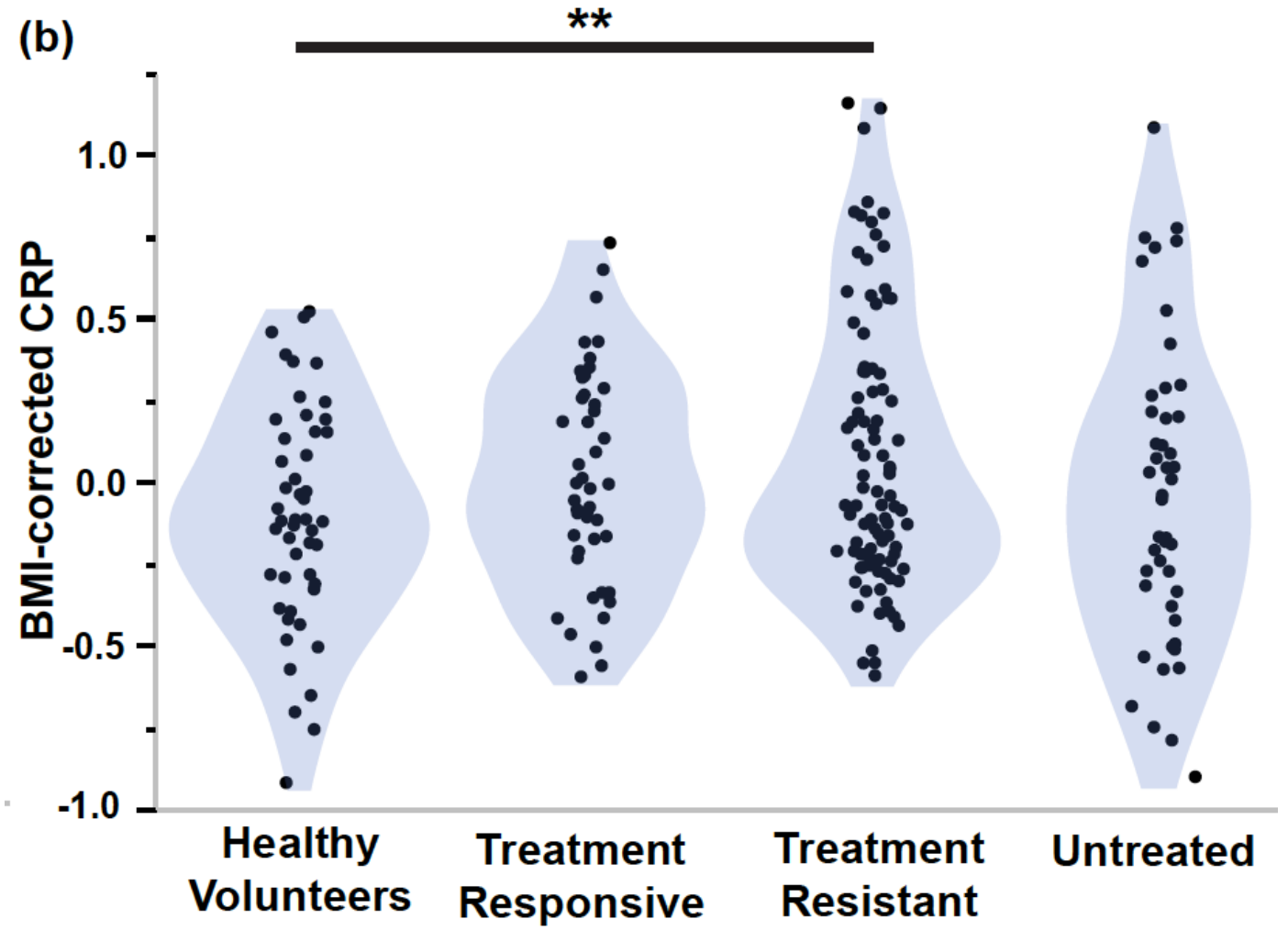
Conclusions

CRP was elevated in patients with MDD, and more so in treatment-resistant patients. Other phenotypes associated with elevated CRP included childhood adversity and specific depressive and anxious symptoms. We suggest that patients with MDD stratified for proinflammatory biomarkers, like CRP, have a distinctive clinical profile that might be responsive to second-line treatment with anti-inflammatory drugs.

Declaration of interest

S.R.C. consults for Cambridge Cognition and Shire; and his input in this project was funded by a Wellcome Trust Clinical Fellowship (110049/Z/15/Z). E.T.B. is employed half time by the University of Cambridge and half time by GlaxoSmithKline; he holds stock in GlaxoSmithKline. In the past 3 years, P.J.C. has served on an advisory board for Lundbeck. N.A.H. consults for GlaxoSmithKline. P.d.B., D.N.C.J. and W.C.D. are employees of Janssen Research & Development, LLC., of Johnson & Johnson, and hold stock in Johnson & Johnson. The other authors report no financial disclosures or potential conflicts of interest.

CRP Levels in Depressed Patients from the NIMA Consortium



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Molecular Psychiatry (2015), 1–8

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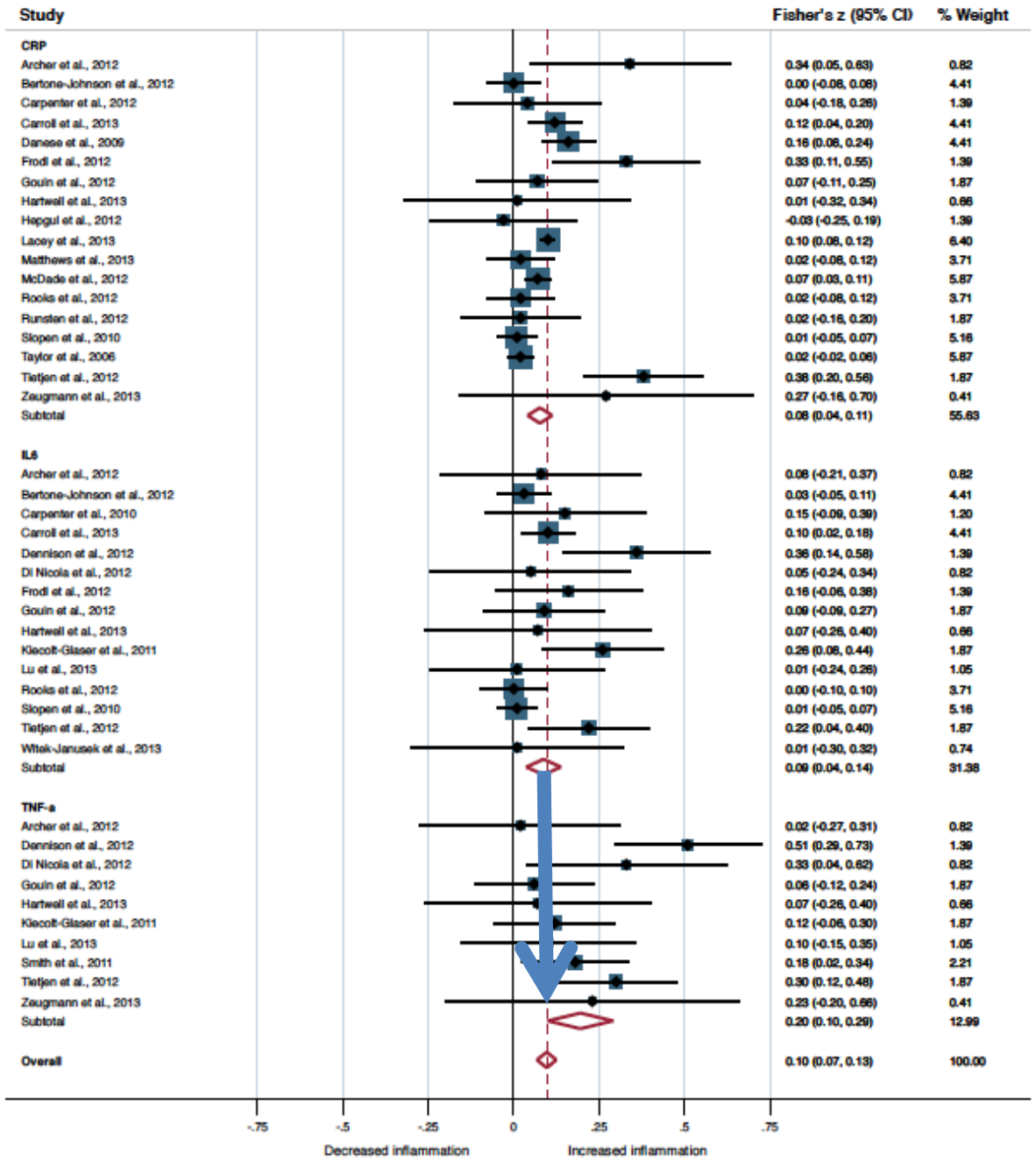
ORIGINAL ARTICLE

Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α

D Baumeister[1,2], R Akhtar[3], S Ciufolini[4,5], CM Pariante[1] and V Mondelli[1,5]

Childhood trauma confers higher risk of adulthood physical and mental illness; however, the biological mechanism mediating this association remains largely unknown. Recent research has suggested dysregulation of the immune system as a possible biological mediator. The present paper conducted a meta-analysis to establish whether early-life adversity contributes to potentially pathogenic pro-inflammatory phenotypes in adult individuals. A systematic search of Pubmed, PsycINFO, EMBASE, Scopus and Medline identified 25 articles for the meta-analysis, including 18 studies encompassing a sample of 16 870 individuals for C-reactive protein (CRP), 15 studies including 3751 individuals for interleukin-6 (IL-6) and 10 studies including 881 individuals for tumour necrosis factor-α (TNF-α). Random-effects meta-analysis showed that individuals exposed to childhood trauma had significantly elevated baseline peripheral levels of CRP (Fisher's $z = 0.10$, 95% confidence interval (CI) = 0.05–0.14), IL-6 ($z = 0.08$, 95% CI = 0.03–0.14) and TNF-α ($z = 0.23$, 95% CI = 0.14–0.32). Subgroup analyses for specific types of trauma (sexual, physical or emotional abuse) revealed that these impact differentially the single inflammatory markers. Moreover, meta-regression revealed greater effect sizes in clinical samples for the association between childhood trauma and CRP but not for IL-6 or TNF-α. Age, body mass index (BMI) and gender had no moderating effects. The analysis demonstrates that childhood trauma contributes to a pro-inflammatory state in adulthood, with specific inflammatory profiles depending on the specific type of trauma.

Molecular Psychiatry advance online publication, 2 June 2015; doi:10.1038/mp.2015.67


Study
Fisher's z (95% CI)
% Weight
CRP
Archer et al., 2012 0.34 (0.05, 0.63) 0.82
Bertone-Johnson et al., 2012 0.00 (-0.08, 0.08) 4.41
Carpenter et al., 2012 0.04 (-0.18, 0.26) 1.39
Carroll et al., 2013 0.12 (0.04, 0.20) 4.41
Danese et al., 2009 0.16 (0.08, 0.24) 4.41
Frodl et al., 2012 0.33 (0.11, 0.55) 1.39
Goulin et al., 2012 0.07 (-0.11, 0.25) 1.87
Hartwell et al., 2013 0.01 (-0.32, 0.34) 0.66
Hepgul et al., 2012 -0.03 (-0.25, 0.19) 1.39
Lacey et al., 2013 0.10 (0.08, 0.12) 6.40
Matthews et al., 2013 0.02 (-0.08, 0.12) 3.71
McDade et al., 2012 0.07 (0.03, 0.11) 5.87
Rooks et al., 2012 0.02 (-0.08, 0.12) 3.71
Runsten et al., 2012 0.02 (-0.16, 0.20) 1.87
Slopen et al., 2010 0.01 (-0.05, 0.07) 5.16
Taylor et al., 2006 0.02 (-0.02, 0.06) 5.87
Tietjen et al., 2012 0.38 (0.20, 0.56) 1.87
Zeugmann et al., 2013 0.27 (-0.16, 0.70) 0.41
Subtotal 0.08 (0.04, 0.11) 55.83
IL6
Archer et al., 2012 0.08 (-0.21, 0.37) 0.82
Bertone-Johnson et al., 2012 0.03 (-0.05, 0.11) 4.41
Carpenter et al., 2010 0.15 (-0.09, 0.39) 1.20
Carroll et al., 2013 0.10 (0.02, 0.18) 4.41
Dennison et al., 2012 0.36 (0.14, 0.58) 1.39
Di Nicola et al., 2012 0.05 (-0.24, 0.34) 0.82
Frodl et al., 2012 0.16 (-0.06, 0.38) 1.39
Goulin et al., 2012 0.09 (-0.09, 0.27) 1.87
Hartwell et al., 2013 0.07 (-0.26, 0.40) 0.66
Kiecolt-Glaser et al., 2011 0.26 (0.08, 0.44) 1.87
Lu et al., 2013 0.01 (-0.24, 0.26) 1.05
Rooks et al., 2012 0.00 (-0.10, 0.10) 3.71
Slopen et al., 2010 0.01 (-0.05, 0.07) 5.16
Tietjen et al., 2012 0.22 (0.04, 0.40) 1.87
Witek-Janusek et al., 2013 0.01 (-0.30, 0.32) 0.74
Subtotal 0.09 (0.04, 0.14) 31.38
TNF-a
Archer et al., 2012 0.02 (-0.27, 0.31) 0.82
Dennison et al., 2012 0.51 (0.29, 0.73) 1.39
Di Nicola et al., 2012 0.33 (0.04, 0.62) 0.82
Goulin et al., 2012 0.06 (-0.12, 0.24) 1.87
Hartwell et al., 2013 0.07 (-0.26, 0.40) 0.66
Kiecolt-Glaser et al., 2011 0.12 (-0.06, 0.30) 1.87
Lu et al., 2013 0.10 (-0.15, 0.35) 1.05
Smith et al., 2011 0.18 (0.02, 0.34) 2.21
Tietjen et al., 2012 0.30 (0.12, 0.48) 1.87
Zeugmann et al., 2013 0.23 (-0.20, 0.66) 0.41
Subtotal 0.20 (0.10, 0.29) 12.99
Overall 0.10 (0.07, 0.13) 100.00
-.75
-.5
-.25
0
.25
.5
.75
Decreased inflammation
Increased inflammation

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Cortisol and Inflammatory Biomarkers Predict Poor Treatment Response in First Episode Psychosis

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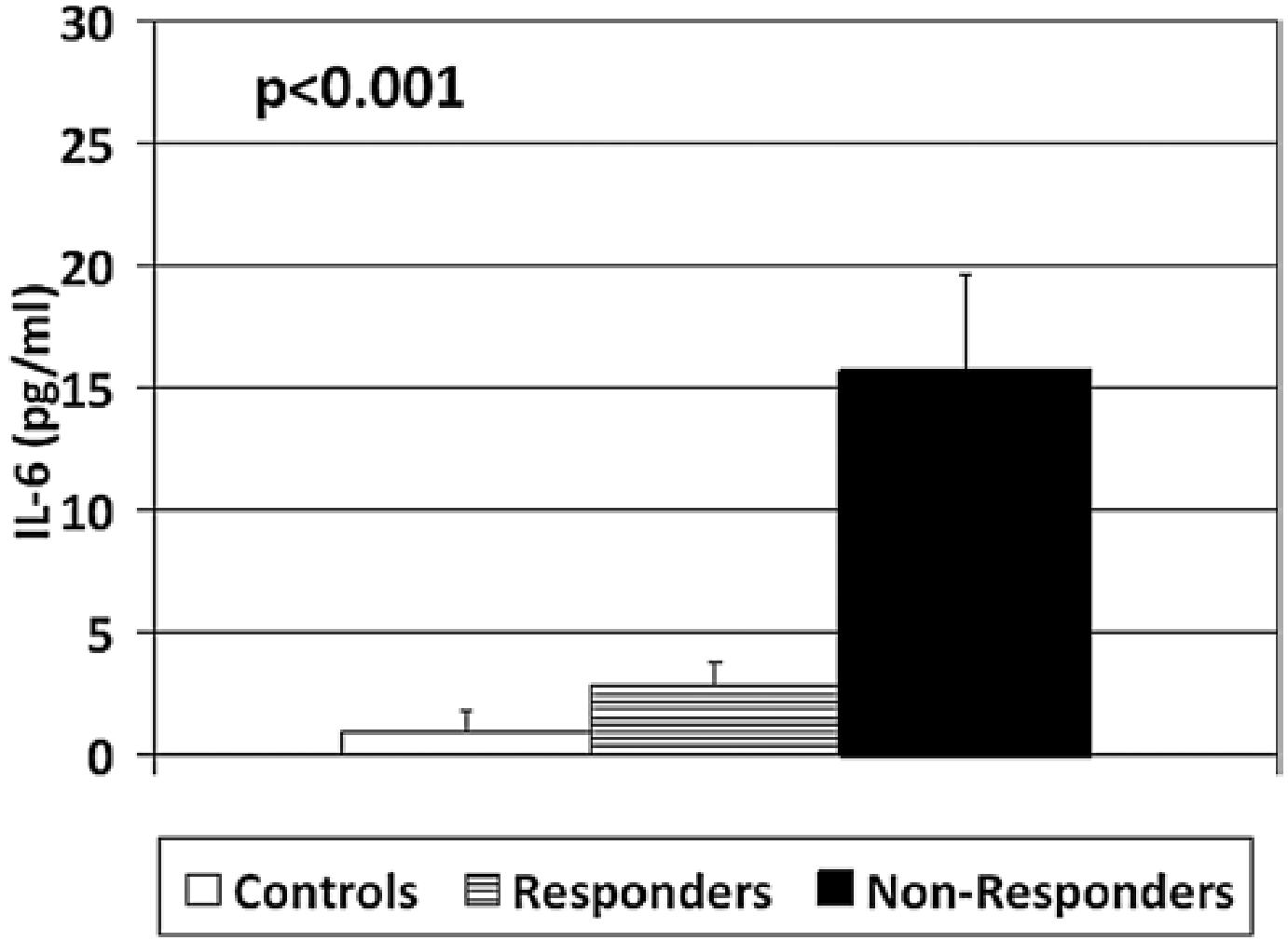
Baseline inflammation and treatment response in psychosis



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Metabolic-inflammatory status as predictor of clinical outcome at 1-year follow-up in patients with first episode psychosis

Maria Antonietta Nettis[a,b,*], Giulio Pergola[c], Anna Kolliakou[d], Jennifer O'Connor[d], Stefania Bonaccorso[d], Anthony David[d], Fiona Gaughran[d,e], Marta Di Forti[f], Robin M. Murray[d,g], Tiago Reis Marques[d], Giuseppe Blasi[c], Alessandro Bertolino[c], Carmine M. Pariante[a,b], Paola Dazzan[d], Valeria Mondelli[a,b]

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Baseline inflammation and treatment response in psychosis

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Metabolic-inflammatory status as predictor of clinical outcome at 1-year follow-up in patients with first episode psychosis

Maria Antonietta Nettis[a,b,*], Giulio Pergola[c], Anna Kolliakou[d], Jennifer O'Connor[d],

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Metabolic-inflammatory status as predictor of clinical outcome at 1-year follow-up in patients with first episode psychosis

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Cortisol, inflammatory biomarkers and neurotrophins in children and adolescents with attention deficit hyperactivity disorder (ADHD) in Taiwan

Jane Pei-Chen Chang[a,b,c], Valeria Mondelli[a], Sentil Kumaran Satyanarayanan[b], Yi-Ju Chiang[b,c], Hui-Ting Chen[b,c], Kuan-Pin Su[a,b,c,d,*], Carmine M. Pariante[a]

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Inflammatory Biomarkers and Neurotrophins in ADHD

Mean (SD)	ADHD	TD	*P*
	(n = 93)	(n = 21)	
Age (yrs)	9.40 (3.08)	9.19 (2.96)	0.779
Gender (male n, %)	81 (87.1)	15 (71.4)	.097[a]
→ BDNF (n = 91 vs 21)	778.81 (380.58)	1224.62 (456.40)	< 0.0001****
bNGF (n = 59 vs 13)	235.54 (372.32)	284.69 (394.90)	0.548[#]
GDNF (n = 54 vs 12)	1538.81 (2981.28)	1650.83 (4475.27)	0.517[#]
→ hs-CRP[$] (n = 89 vs 21)	2.10 (0.95)	1.37 (0.04)	< 0.0001****[#]
IL-1b (n = 71 vs 15)	67.87 (105.80)	99.60 (181.55)	0.597[#]
IL-10 (n = 71 vs 17)	1109.86 (558.56)	936.53 (586.22)	0.259
→ IL-6 (n = 78 vs 20)	266.65 (176.52)	71.15 (89.04)	< 0.0001[@]****
NT-3 (n = 59 vs 12)	624.49 (745.75)	1202.83 (1504.87)	0.365[#]
→ TNFα (n = 71 vs 18)	239.72 (270.50)	426.56 (265.21)	< 0.0001****[#]

Psychoneuroendocrinology 100 (2019) 276–285

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Persistent fatigue induced by interferon-alpha: a novel, inflammation-based, proxy model of chronic fatigue syndrome

Alice Russell[a,*], Nilay Hepgul[a], Naghmeh Nikkheslat[a], Alessandra Borsini[a], Zuzanna Zajkowska[a], Natalie Moll[b], Daniel Forton[c], Kosh Agarwal[d], Trudie Chalder[a,e], Valeria Mondelli[a], Matthew Hotopf[a], Anthony Cleare[a], Gabrielle Murphy[f], Graham Foster[g], Terry Wong[h], Gregor A. Schütze[b], Markus J. Schwarz[b], Neil Harrison[i], Patricia A. Zunszain[a], Carmine M. Pariante[a]

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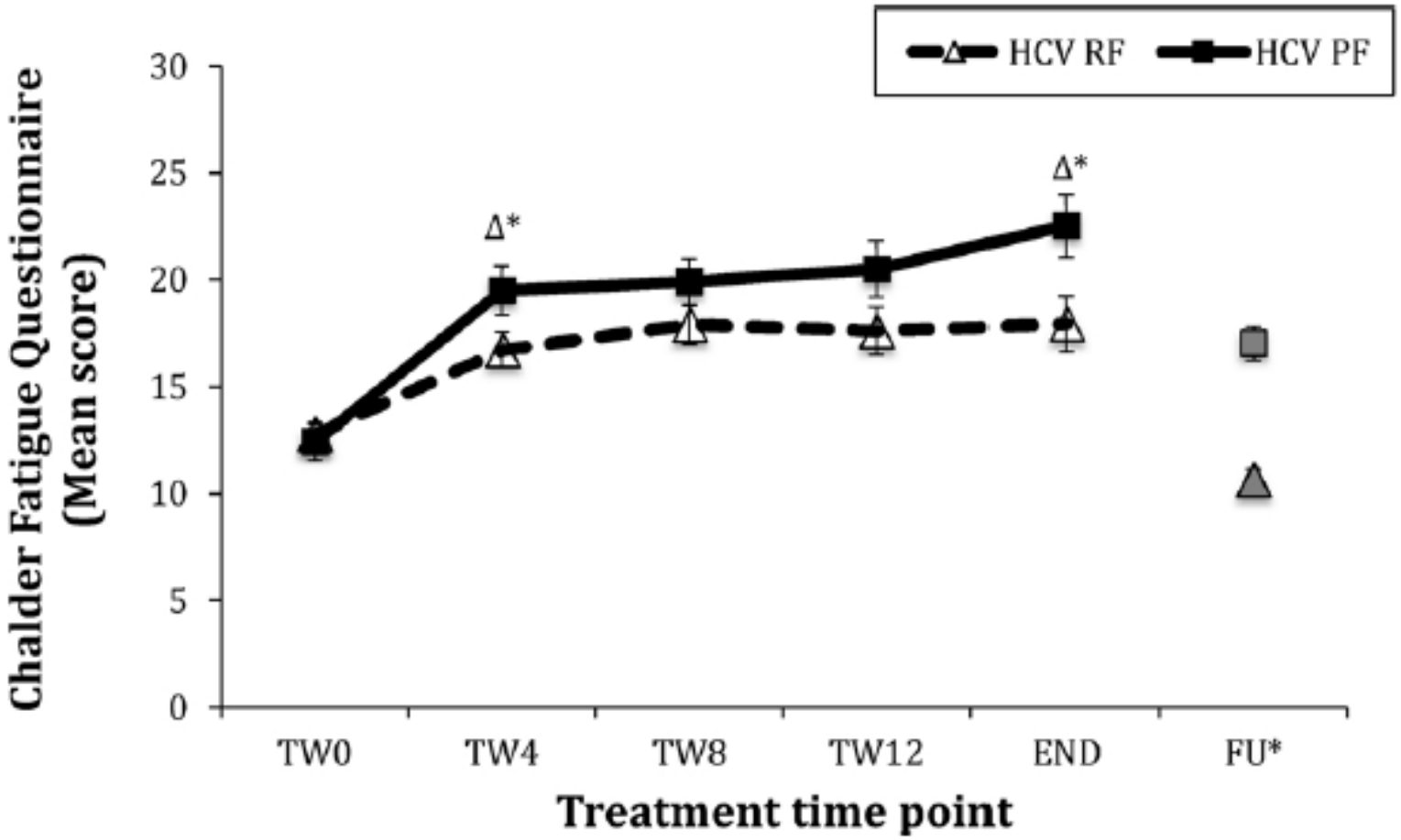
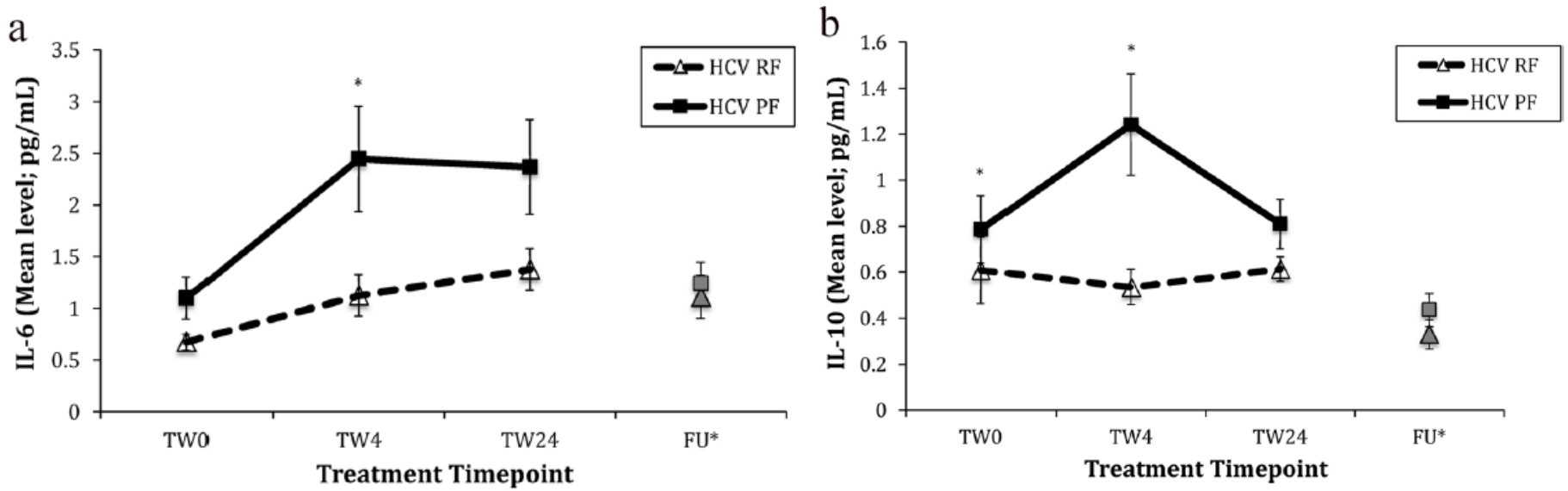
Immune Predictors of Chronic Fatigue-like Syndrome



Immune Predictors of Chronic Fatigue-like Syndrome



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ARTICLE OPEN

Augmentation therapy with minocycline in treatment-resistant depression patients with low-grade peripheral inflammation: results from a double-blind randomised clinical trial

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This study aimed to investigate the role of baseline levels of peripheral inflammation when testing the efficacy of antidepressant augmentation with minocycline in patients with treatment-resistant depression. We conducted a 4-week, placebo-controlled, randomised clinical trial of minocycline (200 mg/day) added to antidepressant treatment in 39 patients selected for elevated levels of serum C-reactive protein (CRP ≥ 1 mg/L), $n = 18$ randomised to minocycline (M) and $n = 21$ to placebo (P). The main outcome was the change in Hamilton Depression Rating Scale (HAM-D-17) score from baseline to week 4, expressed both as mean and as full or partial response, in the overall sample and after further stratification for baseline CRP≥3 mg/L. Secondary outcomes included changes in other clinical and inflammatory measures. Changes in HAM-D-17 scores and the proportion of partial responders did not differ between study arms. After stratification for CRP levels <3 mg/L (CRP^-) or ≥3 mg/L (CRP^+), CRP^+/M patients showed the largest changes in HAM-D-17 scores (mean ± SD = 12.00 ± 6.45) compared with CRP^-/M (2.42 ± 3.20, $p < 0.001$), CRP^+/P (3.50 ± 4.34, $p = 0.003$) and CRP^-/P (2.11 ± 3.26, $p = 0.006$) patients, and the largest proportion (83.3%, $p = 0.04$) of partial treatment response at week 4. The threshold point for baseline CRP to distinguish responders from non-responders to minocycline was 2.8 mg/L. Responders to minocycline had higher baseline IL-6 concentrations than non-responders ($p = 0.03$); IFNγ was significantly reduced after treatment with minocycline compared with placebo ($p = 0.03$). Our data show some evidence of efficacy of add-on treatment with minocycline in MDD patients but only in those with low-grade inflammation defined as CRP ≥3 mg/L.

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INTRODUCTION

Emerging evidence of the role of the immune system in Major Depressive Disorder (MDD) has stimulated a growing interest in exploring the antidepressant properties of anti-inflammatory agents, either as monotherapy or as add-on treatment to

the risk of haemorrhage [6]. Finally, efficacy results are inconsistent, particularly for NSAIDs like COX-2 inhibitors, which, at least in some studies, showed only a modest and non-sustained antidepressant efficacy [7], or may even have an antagonistic effect on the antidepressant actions of selective serotonin reuptake inhibitors [8].