International Journal of Immunopathology & Pharmacology

Editorial

International Journal of Immunopathology and Pharmacology
2016, Vol. 29(4) 583–594

DOI: 10.1177/0394632015623793
iji.sagepub.com
SAGE

Inflammatory markers and suicidal attempts in depressed patients: A review

Stefano Marini,[1] Federica Vellante,[1] Ilaria Matarazzo,[1] Domenico De Berardis,[1,2] Nicola Serroni,[2] Daniela Gianfelice,[2] Luigi Olivieri,[2] Fulvia Di Renzo,[2] Anna Di Marco,[2] Michele Fornaro,[3] Laura Orsolini,[4,5] Alessandro Valchera,[6] Felice Iasevoli,[7] Monica Mazza,[8] Giampaolo Perna,[9,10,11] Giovanni Martinotti[1] and Massimo Di Giannantonio[1]

Abstract

Major depressive disorder is a chronic and invalidating psychiatric illness and is associated with a greater risk of suicidal behaviors. In recent decades many data have supported a biological link between depressive states and inflammation. Pro-inflammatory cytokines have been found to rise, first of all TNF-α and IL-6. Suicidal behaviors have been consistently associated with increased levels of IL-6 and decreased levels of IL-2. The aim of this review is to investigate the relationship between inflammatory markers in depressed patients with or without suicidal attempts compared to healthy controls.

Keywords

inflammatory markers, major depressive disorder, suicidal attempts

Date received: 16 May 2015; accepted: 27 November 2015

Introduction

Major depressive disorder (MDD) is a chronic and invalidating psychiatric illness leading to both social and occupational disability.[1–3] MDD patients show a greater risk of suicidal behaviors than healthy controls (HC).[4–8] Even if suicidal behavior has been classified as a separate diagnosis in the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5),[1] suicide is often associated with co-morbid psychiatric disorders. For these reasons, death by suicide may be avoided following some suicide prevention strategies;[9] for systematic review and meta-analysis see Brezo et al.[10] and Arsenault-Lapierre et al.[11]

Inflammation and stressor mediators leading to excitotoxicity and oxidative damage seem to play a critical role in the pathophysiology of MDD. Different cytokines have been identified as potentially relevant in the understanding of the link between mood disorders and suicidality. In fact, untreated depressed patients have been found to present an imbalance among pro-inflammatory

[1]Department of Neurosciences and Imaging, Chair of Psychiatry, University "G. D'Annunzio", Chieti, Italy
[2]NHS, Department of Mental Health, Psychiatric Service of Diagnosis and Treatment, Hospital "G. Mazzini", ASL 4 Teramo, Italy
[3]Department of "Scienze della Formazione", University of Catania, Italy
[4]United Hospitals, Academic Department of Experimental and Clinical Medicine, Polytechnic University of Marche, Ancona, Italy
[5]School of Life and Medical Sciences, University of Hertfordshire, Hatfield, Herts, UK
[6]Villa S. Giuseppe Hospital, Hermanas Hospitalarias, Ascoli Piceno, Italy
[7]Laboratory of Molecular Psychiatry and Psychopharmacotherapeutics, Section of Psychiatry, Department of Neuroscience, University School of Medicine "Federico II", Naples, Italy
[8]Department of Health Science, University of L'Aquila, L'Aquila, Italy
[9]Hermanas Hospitalarias, Department of Clinical Neurosciences, Villa San Benedetto Menni, Albese con Cassano, Como, Italy
[10]Department of Psychiatry and Behavioral Sciences, Leonard Miller School of Medicine, University of Miami, Florida, USA
[11]Department of Psychiatry and Neuropsychology, University of Maastricht, The Netherlands

Corresponding author:
Stefano Marini, Department of Neurosciences and Imaging, Chair of Psychiatry, University "G. d'Annunzio", via Dei Vestini, 66100 Chieti, Italy.
Email: sfnmarini@gmail.com

cytokines, such as interleukin-1β (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), interferon-γ (IFN-γ) and tumour necrosis factor-α (TNF-α).[12–14] In addition, various immunomodulators have been used to treat subclinical symptoms of depression, such as pain and fatigue, and sexual, bladder and bowel dysfunctions.[15]

A family history of suicide is considered a risk and a predictive factor of suicidality in offspring. Contrary to suicidal behaviour, suicidal thoughts do not seem to be directly linked to a family history of suicidal ideation.[16,17]

Genetic studies have also tried to build a solid theoretical basis on gene-related aspects of suicide. Particular attention has been given to the gene encoding for tryptophan hydroxylase and monoamine oxidase A;[18,19] for a review see Brezo et al.[20]

Early-life adversities (ELA) are considered as important lifetime risks for suicidal behaviour. In fact, recent research has suggested a link between poor parent–child attachment and maladjustment in the parental role on one side, and childhood abuse on the other.[21,22]

Altered blood levels of serotonin seem to underlie depressive and suicide risk factors. Coupling postmortem binding studies and *in vivo* studies using positron emission tomography highlighted altered 5-hydroxytryptamine 1A and 2A (5HT1A, 5HT2A) receptor availability in suicidal brains, suggesting that insufficient serotonin levels in certain areas of the brain may be linked to suicidality.[4,5,23] Serotonin variation has also been considered specific to suicidal behaviour, but this alteration shows only a partial overlapping in those with depressed brains.[24,25] In addition, it has been found that different serotoninergic genes contribute jointly to increase the risk for depression and suicidal behaviours.[26,27] Moreover, a lower serotoninergic neurotransmission has been associated with behaviour related to suicide attempts, such as impulsive and aggressive traits, irrespective of other psychiatric conditions. Variations in serotonin levels are associated with the onset of depressive and suicidal symptoms in euthymic individuals who have had previous depressive episodes, and in patients at higher risk for developing depression.[28,29]

Stressors derived from different origins, such as physical, emotional or hormonal stimuli, physiologically activate the same pathway of polyamine, named the polyamine stress response system. Protein levels of several components of the polyamine are altered in the cortical and subcortical brain regions in patients who had completed suicide and in psychiatric patients dead from other causes.[30,31]

Primate models of depression suggest that stress may induce a modification in gene expression, leading to alterations of spermidine and spermine N1-acetyltransferase (SAT1), wich is considered the rate-limiting enzyme in the catabolism of polyamines. SAT1 has been found to be decreased in the brain cortex of suicide completers, and has been considered a peripheral biomarker of suicidality.[32–34]

In recent decades many data have supported a biological link between depressive states and inflammation. An increase of pro-inflammatory cytokines have been highlighted, mainly of TNF and IL-6.[35–37] Moreoveor, patients undergoing therapy with IFN-α have been found to often develop mood depression.[38] Several reports show an association between suicidal behaviour and inflammatory cytokines even in the absence of depressive mood. Suicidal behaviour has been consistently associated with increased levels of IL-6 and decreased levels of IL-2. Decreased levels of vascular endothelial growth factor (VEGF) and increased levels of quinolonic and kinurenic acids have also been described in suicidal depressed patients.[39,40] A higher peripheral inflammatory chemokine concentration has been reported in individuals with MDD and suicidal ideation than in those without suicidal ideation.[41,42] Moreover, some authors reported data about the relationship among alexithymia, suicidal ideation and C-reactive protein,[43] and data regarding the effects of antidepressants on cytokine concentrations (for a review see De Berardis et al.[44]).

With respect to GABAergic signaling, it seems that the genes encoding GABA type A receptors subunits and their associated binding proteins may be be upregulated in the hippocampus and in the prefrontal and anterior cingulate cortices of suicidal depressed patients.[45,46] For these reasons, agents acting on the glutamatergic way are considered rapid-response antidepressants, useful in the treatment of both depressive mood and acute suicidal ideation.[47,48]

Many studies have analysed the role of astrocytes in psychopathology. In animal models of depression, impaired glial functions have been reported.[49,50] Postmortem brain studies indicated a decreased glial cell count in the cortical grey matter of depressed patients[51] and hypertrophied astrocytes in the cortical white matter of depressed patients who died by suicide.[52] Expression gene studies have focused on the expression of connexin 30 (CX30) and connexin 43 (CX43), two proteins working as gap junctions and present almost only in astrocyte cells. In animal studies conducted on mice, CX30 and CX43 have shown altered reactivity to novel environment and they have been related to changes in brain neurotransmitters, including serotonin.[53,54]

In individuals attempting and/or completing suicide, evidence of hypothalamus pituitary adrenal (HPA) axis disfunction has been found. Postmortem studies of suicide completers revealed an increased corticotropin-releasing hormone (CRH) activity in the paraventricular nucleus,[55–57] an over-expression of CRH in the cerebrospinal fluid (CSF),[58] fewer CRH-binding sites in the frontal cortex, decreased glucocorticoid receptor expression in the hippocampus and increased levels of pro-opiomelanocortin (POMC) in the pituitary gland.[59,60] In addition, suicide completers show increased adrenal glands weight and adrenocortical hypertrophy. Studies on relatives of suicide attempters highlighted an altered HPA axis response as well.[61–63]

Brain-derived neurotrophic factor (BDNF) was found to be under-expressed by hyper-methylation in stressful situations in studies involving suicide completers. Methylation studies in hippocampal cells taken from patients who died as complete suiciders and who had history of ELA show that ELA was associated with different methylation levels of genes involved in neuroprotection and neuronal growth.[64,65] In pheripheral samples of living patients a different level of methylation in neuronal plasticity genes has also been suggested.[66] These data are similar to those derived from animal studies, supporting an early-life environmental role in regulating genes related to neuronal plasticity. One of them is the gene coding BDNF. In female rodents stressed by introduction into a new environment with inadequate bedding material, the expression of BDNF gene was decreased in prefrontal cortex due to hyper-methylation of BDNF promoter gene.[67] Similar effects were found in the dorsal hippocampus in a post-traumatic stress disorder adult rat model.[68]

In vivo studies on suicide completers showed that they have higher levels of methylation in the Wernicke area than HC. This higher methylation was associated with lower BDNF expression. In line with these data, some studies reported differential methylation of BDNF promoter in pheripheral samples of depressed living patients.[69–72]

Discussion

The aim of this review is to investigate the relationship between inflammatory markers in depressed patients with or without suicidal attempts and suicidal ideation, compared to HC (Table 1). Studies have been divided into three classes: *in vivo*, *in vitro* and postmortem. In each class, when it was possible, studies have been subdivided in: suicidal versus non-suicidal depressed patients and suicidal depressed patients versus HC (for recent systematic reviews and meta-analyses see Serafini et al.,[73] Ducasse et al.[74] and Black and Miller[75]).

In vivo studies

When suicidal depressed patients were compared to non-suicidal depressed patiens, no significant differences in IL-4, IFN-γ and TGF-1β plasma concentrations were found by Gabbay et al.[93] Contrasting results were reported for TNF-α plasma levels.[76,94] O'Donovan[95] found higher IL-6 and CRP plasma levels in patients with higher suicidal ideation than in patients with less suicidal thoughts. A non-significant trend was found for IL-10.[78] Decreased IL-2 plasma concentrations were reported in one study.[78] Increased plasma levels[77] and non-significant group differences[76] were found for IL-6.

Janelidze et al.[77] found increased TNF-α plasma levels in suicidal patients compared to HC. No significant groups differences were reported for TNF-α plasma[76,78] and CSF[96] concentrations. No significant groups differences were reported for IL-4,[76] TGF-1β[76,78] plasma levels and IL-1β[79] CSF levels. Regarding IL-6, two authors reported no

Table 1. Studies investigated in the review.

Authors	Population	Inflammatory markers	*In vivo*/*in vitro* plasma/ CSF postmortem	Scales	Main findings
Gabbay et al.[93]	12 suicidal depressed adolescents, 18 non-suicidal depressed adolescents, 15 controls	IL-1β, IL-4, IL-6, TNF-α, IFN-γ	*In vivo* plasma	CDRS-R, K-SADS-PL, CGAS, BDI-II, BSS	Decreased TNF-α plasma levels in suicidal depressed adolescents and non-suicidal depressed patients. Increased IFN-γ plasma levels in suicidal and non-suicidal versus controls.
Lindqvist et al.[96]	63 suicide attempters, 47 controls	IL-1β, IL-6, IL-8, TNF-α	*In vivo* CSF	MADRS, SUAS	Significantly higher CSF IL-6 levels in suicide attempters than controls. Violent suicide attempters showed the highest IL-6. Significant positive correlation between MADRS scores and CSF IL-6 levels in all patients.
Janelidze et al.[94]	47 suicide attempters, 17 non-suicidal depressed patients, 16 controls	IL-2, IL-6, IL-8, TNF-α	*In vivo* plasma	BSA, MADRS, SUAS, CPRS	Increased levels of IL-6, TNF-α and decreased IL-2 concentrations in suicide attempters compared to non-suicidal depressed patients and controls.
Isung et al.[40]	43 suicide attempters, 20 controls	IL-8, VEGF	*In vivo* CSF	MADRS, SCID	Lower CSF VEGF and IL-8 levels in suicide attempters than controls. A more severe depressive state was correlated with low CSF levels of VEGF.
Vargas et al.[98]	150 patients with a history of suicide attempts, 201 without suicide attempts	IL-6, TNF-α, CRP, fibrinogen, ERS	*In vivo* serum	SCID, ASSIST, self-reported questionnaire for smoking status and lifetime suicidal behavior information	No significant differences between both groups in CRP, fibrinogen, ERS, IL-6 and TNF-α.
O'Donovan et al.[95]	76 depressed patient, 48 controls	IL-6, IL-10, TNF-α, TGF-1β, CRP	*In vivo* plasma	HDRS, MINI	In our sample, patients with MDD who had high levels of suicidal ideation showed significantly elevated IL-6 and CRP levels in high suicidal depressed patients than in low suicidal depressed patients. Only those patients with high levels of suicidal ideation exhibited significantly higher levels of inflammation than controls.
Janelidze et al.[97]	206 suicide attempters, 578 controls	IL-8	*In vivo* CSF and plasma	SCID, CPRS, MADRS, BSA	Significantly lower of IL-8 plasma and CSF levels in suicide attempters with anxiety than in controls. IL-8 plasma and CSF levels correlated negatively with symptoms of anxiety.
Mendlovic et al.[102]	6 suicidal depressed patients, 3 non-suicidal depressed patients, 9 controls	IL-2, IL-4,IL-5, IL-10, IFN- γ	*In vitro* plasma	HDRS, BDI,	Suicidal depressed patients secreted significantly more IFN-γ than controls. Non-suicidal depressed patients secreted significantly less IFN-γ than controls. Suicidal depressed patients secreted less IL-4 and IL-5 than non-suicidal depressed patients (not statistically significant difference).
Lee and Kim[105]	48 suicidal depressed patients, 47 non-suicidal depressed patients, 91 controls	TGF-1β, IL-12,	*In vitro* plasma	HDRS, BPRS	TGF-1β levels were significantly higher in suicidal and non-suicidal depressed patients than in controls.
Kim et al.[103]	36 suicidal depressed patients, 33 non-suicidal depressed patients, 40 controls	IL-2, IL-4, IL-6, IFN-γ, TGF-1β	*In vitro* plasma	HDRS, RRR, LSARS-II	Significantly higher IL-6 levels in non-suicidal depressed patients than suicidal depressed patients and controls. Significantly lower IL-2 levels in suicidal depressed patients than non-suicidal patients and controls. Lower IFN-γ and IL-4 as well as higher TGF-1β in both patients groups. Significant positive correlations between IL-6, IFN-γ and HDRS scores. Significant negative correlations between IL-4 and HDRS scores in non-suicidal depression patients but not in suicidal depressed patients.

Table 1. (Continued)

Authors	Population	Inflammatory markers	*In vivo*/*in vitro* plasma/ CSF postmortem	Scales	Main findings
Lee et al.[104]	124 suicidal depressed patients, 61 non-suicidal depressed patients, 125 controls	TGF-1β	*In vitro* plasma	HDRS, RRR, LARS-II	Significantly higher *in vitro* TGF-1β levels in depressed patients than in controls.
Tonelli et al.[108]	34 completed suicides, 17 controls	–	Postmortem	–	Respectively increased expression of IL-4 and IL-13 in female and male suicide victims.
Boehm et al.[107]	40 suicidal burn victims, 48 non-suicidal deaths for burns, haemorrhagic shock, railway deaths	IL-8, TNF-α, ICAM-1	Postmortem	–	Significantly stronger positivity of TNF-α in burn victims versus controls.
Pandey et al.[106]	24 teenage suicide victims, 24 teenage controls	TNF-α, IL-1β, IL-6 in Brodmann area	Postmortem	–	Significantly increased IL-1β, IL-6 and TNF-α levels in Brodmann area of suicide victims compared with controls.
Nassberger and Traskman-Bendz[101]	Medication-free suicide attempters	IL-2 soluble receptor	*In vivo* plasma, 24-h urine and CSF, follow-up study	–	High levels of the soluble IL-2 receptor concentration at follow-up in medication-free suicide attempters.
Isung et al.[99]	58 suicidal attempters	IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, IFN-γ, VEGF	*In vivo* plasma, longitudinal study	MADRS, SIS	Suicidal patients who completed suicide had lower VEGF levels than suicidal attempters.
Li et al.[100]	49 responder depressed patients, 12 non-responder depressed patient, 64 controls	TNF-α	*In vivo* plasma, longitudinal study	HDRS, SCID	Plasma TNF-α levels significantly decreased in responder patients following venlafaxine treatment. A greater reduction in TNF-α levels correlated to a greater reduction in HDRS scores.

CDRS-R, Children's Depression Rating Scale-Revised;[76] K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version;[77] CGAS, Children's Global Assessment Scale;[78] BDI, Beck Depression Inventory;[79] BSS, Beck Scale for Suicide Ideation;[80] MADRS, Montgomery-Asberg Depression Rating Scale;[81] SUAS, Suicide Assessment Scale;[82] BSA, Brief Scale for Anxiety;[83] CPRS, Comprehensive Psychopathological Rating Scale;[81] SCID, Structured Clinical Interview for DSM-IV;[84,85] ASSIST, The alcohol, smoking and substance involvement screening test;[86] MINI, Mini International Neuropsychiatric Instrument;[87] HDRS, Hamilton Depression Rating Scale;[88] BPRS, Brief Psychiatry Rating Scale;[89] RRR, Risk-Rescue Rating;[90] LARS-II, Lethality Suicide Attempt Rating Scale-updated.[91,92]

significant differences between groups in plasma[76] and CSF concentrations.[40] Three authors found increased IL-6 plasma[77,78] and CSF[79] levels. Increased IFN-γ[76] and IL-10 plasma levels were reported.[78] Lower concentrations were reported for plasma IL-2[77] and CSF VEGF[80] levels. CSF IL-8 concentrations were lower[80] or non-significant.[79] In particular, Janelidze et al.[97] found lower CSF and plasma IL-8 concentrations in suicidal attempters with anxiety. Finally, Vargas et al.[98] reported no significant differences between patients with and without a history of suicide in CRP, fibrinogen, erythrocyte sedimentation rate (ERS), IL-6 and TNF-α.

Some authors reported correlations between cytokine levels and psychopathological scales scores. A positive correlation between Montgomery Asberg Depression Rating Scale (MADRS)[81] scores and CSF IL-6 levels was highlighted in all patients.[79] In particular, violent suicidal attempters showed the highest IL-6 levels.[79] Significant negative correlations between CSF VEGF levels and MADRS scores, and non-significant correlations between CSF IL-8 and MADRS scores were found by Isung et al.[80]

Some longitudinal studies reported data about VEGF, IL-2, IFN-γ and TNF-α levels. Suicidal patients who completed suicide had lower VEGF levels than suicidal attempters, but only a trend for lower IL-2 and IFN-γ levels was found.[99] Plasma TNF-α levels were significantly decreased, in responder patients treated with venlafaxine. The reduction in TNF-α levels was positively related to the reduction in Hamilton Depression Rating Scale (HDRS)[88] scores.[100] Nassberger and Traskman-Bendz[101] found high levels of soluble IL-2 receptor concentration at follow-up in medication-free suicidal attempters.

In vitro studies

Suicidal depressed patients secreted less IL-4, IL-5,[102] IL-2 and IL-6[103] than non-suicidal depressed patients.

The *in vitro* TGF-1β production was significantly higher in depressed patients, both with and without attempted suicide, than in HC,[88,104] but no statistically significant differences were reported by Lee and Kim.[105] Stimulated lymphocytes of suicidal depressed patients secreted significantly more IFN-γ,[87] IL-12[90] and IL-6[88] than those of HC. A lower production of IFN-γ and IL-4 in depressed patients, with or without attempted suicide, compared to HC were reported by Kim et al.[88]

Studies reported different correlations between cytokine concentrations and psychopathological scales scores: positive correlations among IL-6, IFN-γ and HDRS scores;[88] negative correlations between IL-4 and HDRS scores;[88] no correlations between IL-2 or TGF-1β levels and HDRS or Brief Psychiatry Rating Scale (BPRS)[89] scores.[90]

Postmortem studies

In post-mortem studies,[106–108] authors demonstrated associations between inflammatory cytokines and patients dead by suicide (even if most authors, except for Pandey et al., did not report whether patients were depressed or not), when compared to HC. Levels of IL-1β, IL-6 (in adolescents),[92] IL-4 (in women) and IL-13 (in men)[94] were significantly increased in postmortem brain samples of suicide victims compared to those of HC.[93] TNF-α levels resulted also significantly increased, except for Tonelli et al.[94]

For a final summary see Table 2.

Conclusions

In the past few years, a number of studies have been performed in order to identify a biological marker associated with suicidal depressed patients. This review summarises the studies investigating the relationship between inflammatory markers in depressed patients, with or without suicidal attempts and suicidal ideation, in comparison to healthy controls. More studies have been conducted under *in vivo* than *in vitro* and in postmortem conditions. Some, but limited, data reported correlations between cytokine levels and psychopathological scales scores. Insufficient and contrasting data are available in literature so far. For these reasons, furher investigations are needed.

Table 2. Final summary.

Main findings					
Inflammatory markers	Suicidal versus non-suicidal depressed patients		Suicidal depressed patients versus controls		Postmortem suicidal patients versus controls
	In vivo	*In vitro*	*In vivo*	*In vitro*	
IL-4	No significant differences[23]	Decreased[33]	No significant differences[23]	Decreased[34]	Increased[37]
IL-1β	–	–	No significant differences[26]	–	Increased[37]
IFN-γ	No significant differences[23]	–	Increased[23]	Increased[34] Decreased[34]	–
IL-8	–	–	Decreased[27] No significant differences[26] Decreased in anxiety[28]	–	–
IL-6	Increased[24,25] No significant differences[23]	Decreased[33]	No significant differences[23,27,29] Increased[24–26]	Increased[34]	Increased[37]
IL-10	No significant differences[25]	–	Increased[25]	–	–
TGF-1β	No significant differences[23]	–	No significant differences[23,25]	Increased[34,35] No significant differences[36]	–
IL-2	Decreased[24]	Decreased[33]	Decreased[24]	–	–
IL-12	–	–	–	Increased[36]	–
IL-5	–	Decreased[33]	–	–	–
TNF-α	Increased[23] Decreased[24]	–	Increased[24] No significant differences[23,25] No significant differences[26]	–	Increased[37,38] No significant differences[39]
CRP	Increased[25]	–	No significant differences[29]	–	–
VEGF	–	–	Decreased[24]	–	–
ERS	–	–	No significant differences[29]	–	–
Fibrinogen	–	–	No significant differences[29]	–	–
IL-13	–	–	–	–	Increased[39]

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington, DC: American Psychiatric Publishing.
2. Réka S, Zoltán J and Kálmán J (2012) The blue side of glutamatergic neurotransmission: NMDA receptor antagonists as possible novel therapeutics for major depression. *Neuropsychopharmacologia Hungarica* 14: 29–40.
3. Greer TL, Kurian BT and Trivedi MH (2010) Defining and measuring functional recovery from depression. *CNS Drugs* 24: 267–284.
4. Pompili M, Serafini G, Innamorati M, et al. (2011) Suicide risk in first episode psychosis: A selective review of the current literature. *Schizophrenia Research* 129: 1–11.
5. Pompili M, Innamorati M, Rihmer Z, et al. Cyclothymic-depressive anxious temperament pattern is related to suicide risk in 346 patients with major mood disorders. *Journal of Affective Disorders* 136: 405–411.
6. Pompili M, Rihmer Z, Akiskal H, et al. (2012) Temperaments mediate suicide risk and psychopathology among patients with bipolar disorders. *Comprehensive Psychiatry* 53: 280–285.
7. Serafini G, Pompili M, Innamorati M, et al. (2011) Affective temperamental profiles are associated with white matter hyperintensity and suicidal risk in patients with mood disorders. *Journal of Affective Disorders* 129: 47–55.
8. Innamorati M, Pompili M, Gonda X, et al. (2011) Psychometric properties of the Gotland Scale for Depression in Italian psychiatric inpatients and its utility in the prediction of suicide risk. *Journal of Affective Disorders* 132: 99–103.
9. Mann JJ, Apter A, Bertolote J, et al. (2005) Suicide prevention strategies: A systematic review. *Journal of the American Medical Association* 294: 2064–2074.
10. Brezo J, Paris J, Tremblay R, et al. (2007) Identifying correlates of suicide attempts in suicidal ideators: A population-based study. *Psychological Medicine* 37: 1551–1562.
11. Arsenault-Lapierre G, Kim C and Turecki G (2004) Psychiatric diagnoses in 3275 suicides: A meta-analysis. *BMC Psychiatry* 4: 37.
12. Ackerman KD, Martino M, Heyman R, et al. (1998) Stressor induced alteration of cytokine production in multiple sclerosis patients and controls. *Psychosomatic Medicine* 60: 484–491.
13. Maes M (1999) Major depression and activation of the inflammatory response system. *Advances in Experimental Medicine and Biology* 461: 25–46.
14. Maes M, Meltzer HY, Bosmans E, et al. (1995) Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin- 2 and transferring receptor in major depression. *Journal of Affective Disorders* 34: 301–309.
15. Krupp LB and Rizvi SA (2002) Symptomatic therapy for underrecognized manifestations of multiple sclerosis. *Neurology* 58: S32–39.
16. Lieb R, Bronisch T, Hofler M, et al. (2005) Maternal suicidality and risk of suicidality in offspring: Findings from a community study. *American Journal of Psychiatry* 162: 1665–1671.
17. Blum R, Sudhinaraset M and Emerson MR (2012) Youth at risk: Suicidal thoughts and attempts in Vietnam, China, and Taiwan. *Journal of Adolescent Health* 50: S37–S44.
18. Mann JJ (2013) The serotonergic system in mood disorders and suicidal behaviour. *Philosophical Transactions of the Royal Society of London Series B* 368: 20120537.
19. Bach H and Arango V (2012) Neuroanatomy of serotonergic abnormalities in suicide. In: Dwivedi Y (ed) *The Neurobiological Basis of Suicide*. Boca Raton, FL: CRC Press, pp. 15–17.
20. Brezo J, Klempan T and Turecki G (2008) The genetics of suicide: A critical review of molecular studies. *Psychiatric Clinics of North America* 31: 179–203.
21. Fergusson DM, Woodward LJ and Horwood LJ (2000) Risk factors and life processes associated with the onset of suicidal behaviour during adolescence and early adulthood. *Psychological Medicine* 30: 23–39.
22. Smith PN, Gamble SA, Cort NA, et al. (2012) The relationships of attachment style and social maladjustment to death ideation in depressed women with a history of childhood sexual abuse. *Journal of Clinical Psychology* 68: 78–87.
23. Stanley M, Virgilio J and Gershon S (1982) Tritiated imipramine binding sites are decreased in the frontal cortex of suicides. *Science* 216: 1337–1339.
24. Arango V, Underwood MD, Boldrini M, et al. (2001) Serotonin 1A receptors, serotonin transporter binding and serotonin transporter mRNA expression in the brainstem of depressed suicide victims. *Neuropsychopharmacology* 25: 892–900.
25. Miller JM, Hesselgrave N, Ogden RT, et al. (2013) Positron emission tomography quantification of serotonin transporter in suicide attempters with major

depressive disorder. *Biological Psychiatry* 74: 287–295.
26. Yanowitch R and Coccaro EF (2011) The neurochemistry of human aggression. *Advances in Genetics* 75: 151–169.
27. Brezo J, Bureau A, Mérette C, et al. (2010) Differences and similarities in the serotonergic diathesis for suicide attempts and mood disorders: A 22-year longitudinal gene–environment study. *Molecular Psychiatry* 15: 831–843.
28. Smith KA, Fairburn CG and Cowen PJ (1997) Relapse of depression after rapid depletion of tryptophan. *Lancet* 349: 915–919.
29. Benkelfat C, Ellenbogen MA, Dean P, et al. (1994) Mood-lowering effect of tryptophan depletion. Enhanced susceptibility in young men at genetic risk for major affective disorders. *Archives of General Psychiatry* 51: 687–697.
30. Sequeira A, Gwadry FG, Ffrench-Mullen JM, et al. (2006) Implication of SSAT by gene expression and genetic variation in suicide and major depression. *Archives of General Psychiatry* 63: 35–48.
31. Chen GG, Fiori LM, Moquin L, et al. (2010) Evidence of altered polyamine concentrations in cerebral cortex of suicide completers. *Neuropsychopharmacology* 35: 1477–1484.
32. Fiori LM, Bureau A, Labbe A, et al. (2011) Global gene expression profiling of the polyamine system in suicide completers. *International Journal of Neuropsychopharmacology* 14: 595–605.
33. Klempan TA, Rujescu D, Mérette C, et al. (2009) Profiling brain expression of the spermidine/spermine N1-acetyltransferase 1 (SAT1) gene in suicide. *American Journal of Medical Genetics Part B Neuropsychiatric Genetics* 150B: 934–943.
34. Karssen AM, Her S, Li JZ, et al. (2007) Stress-induced changes in primate prefrontal profiles of gene expression. *Molecular Psychiatry* 12: 1089–1102.
35. Raison CL, Capuron L and Miller AH (2006) Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends in Immunology* 27: 24–31.
36. Howren MB, Lamkin DM and Suls J (2009) Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. *Psychosomatic Medicine* 71: 171–186.
37. Shelton RC, Claiborne J, Sidoryk-Wegrzynowicz M, et al. (2011) Altered expression of genes involved in inflammation and apoptosis in frontal cortex in major depression. *Molecular Psychiatry* 16: 751–762.
38. Constant A, Castera L, Dantzer R, et al. (2005) Mood alterations during interferon-α therapy in patients with chronic hepatitis C: Evidence for an overlap between manic/hypomanic and depressive symptoms. *Journal of Clinical Psychiatry* 66: 1050–1057.
39. Sublette ME, Galfalvy HC, Fuchs D, et al. (2011) Plasma kynurenine levels are elevated in suicide attempters with major depressive disorder. *Brain Behavior Immunity* 25: 1272–1278.
40. Isung J, Aeinehband S, Mobarrez F, et al. (2012) Low vascular endothelial growth factor and interleukin-8 in cerebrospinal fluid of suicide attempters. *Translational Psychiatry* 2: e196.
41. Grassi-Oliveira R, Brieztke E, Teixeira A, et al. (2002) Peripheral chemokine levels in women with recurrent major depression with suicidal ideation. *Revista Brasileira de Psiquiatria* 34: 71–75.
42. Janelidze S, Ventorp F, Erhardt S, et al. (2013) Altered chemokine levels in the cerebrospinal fluid and plasma of suicide attempters. *Psychoneuroendocrinology* 38(6): 853–862.
43. De Berardis D, Serroni N, Campanella D, et al. (in press) Alexithymia, suicide ideation, C-reactive protein and serum lipid levels among outpatients with generalized anxiety disorder. *Archives of Suicide Research*.
44. De Berardis D, Conti CM, Serroni N, et al. (2010) The effect of newer serotonin-noradrenalin antidepressants on cytokine production: A review of the current literature. *International Journal of Immunopathology and Pharmacology* 23: 417–422.
45. Sequeira A, Mamdani F, Ernst C, et al. (2009) Global brain gene expression analysis links glutamatergic and GABAergic alterations to suicide and major depression. *PLoS One* 4: e6585.
46. Choudary PV, Molnar M, Evans SJ, et al. (2005) Altered cortical glutamatergic and GABAergic signal transmission with glial involvement in depression. *Proceedings of the National Academy of Sciences of the United States of America* 102: 15653–15658.
47. Larkin GL and Beautrais AL (2011) A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. *International Journal of Neuropsychopharmacology* 14: 1127–1131.
48. Price RB, Iosifescu DV, Murrough JW, et al. (2014) Effects of ketamine on explicit and implicit suicidal cognition: A randomized controlled trial in treatment-resistant depression. *Depression and Anxiety* 31: 335–343.
49. Czeh B, Fuchs E and Flugge G (2013) Altered glial plasticity in animal models for mood disorders. *Current Drug Targets* 14: 1249–1261.
50. Banasr M, Chowdhury GM, Terwilliger R, et al. (2010) Glial pathology in an animal model of depression: Reversal of stress-induced cellular, metabolic and behavioral deficits by the glutamate-modulating drug riluzole. *Molecular Psychiatry* 15: 501–511.

51. Rajkowska G (2000) Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. *Biological Psychiatry* 48: 766–777.
52. Torres-Platas SG, Hercher C, Davoli MA, et al. (2011) Astrocytic hypertrophy in anterior cingulate white matter of depressed suicides. *Neuropsychopharmacology* 36: 2650–2658.
53. Dere E, De Souza-Silva MA, Frisch C, et al. (2003) Connexin30-deficient mice show increased emotionality and decreased rearing activity in the open-field along with neurochemical changes. *European Journal of Neuroscience* 18: 629–638.
54. Frisch C, Theis M, De Souza Silva MA, et al. (2003) Mice with astrocyte-directed inactivation of connexin 43 exhibit increased exploratory behaviour, impaired motor capacities, and changes in brain acetylcholine levels. *European Journal of Neuroscience* 18: 2313–2318.
55. Raadsheer FC, van Heerikhuize JJ, Lucassen PJ, et al. (1995) Corticotropin-releasing hormone mRNA levels in the paraventricular nucleus of patients with Alzheimer's disease and depression. *American Journal of Psychiatry* 152: 1372–1376.
56. Raadsheer FC, Hoogendijk WJ, Stam FC, et al. (1994) Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. *Neuroendocrinology* 60: 436–444.
57. Wang SS, Kamphuis W, Huitinga I, et al. (2008) Gene expression analysis in the human hypothalamus in depression by laser microdissection and real-time PCR: The presence of multiple receptor imbalances. *Molecular Psychiatry* 13: 786–799.
58. Nemeroff CB, Widerlöv E, Bissette G, et al. (1984) Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science* 226: 1342–1344.
59. Nemeroff CB, Owens MJ, Bissette G, et al. (1998) Reduced corticotropin releasing factor binding sites in the frontal cortex of suicide victims. *Archives of General Psychiatry* 45: 577–579.
60. Lopez JF, Palkovits M, Arató M, et al. (1992) Localization and quantification of pro-opiomelanocortin mRNA and glucocorticoid receptor mRNA in pituitaries of suicide victims. *Neuroendocrinology* 56: 491–501.
61. Dumser T, Barocka A and Schubert E (1998) Weight of adrenal glands may be increased in persons who commit suicide. *American Journal of Forensic Medicine and Pathology* 19: 72–76.
62. Szigethy E, Conwell Y, Forbes NT, et al. (1994) Adrenal weight and morphology in victims of completed suicide. *Biological Psychiatry* 36: 374–380.
63. McGirr A, Diaconu G, Berlim MT, et al. (2010) Dysregulation of the sympathetic nervous system, hypothalamic-pituitary-adrenal axis and executive function in individuals at risk for suicide. *Journal of Psychiatry & Neuroscience* 35: 399–408.
64. Labonte B, Suderman M, Maussion G, et al. (2012) Genome-wide epigenetic regulation by early-life trauma. *Archives of General Psychiatry* 69: 722–731.
65. Labonte B, Suderman M, Maussion G, et al. (2013) Genome-wide methylation changes in the brains of suicide completers. *American Journal of Psychiatry* 170: 511–520.
66. Weder N, Zhang H, Jensen K, et al. (2014) Child abuse, depression, and methylation in genes involved with stress, neural plasticity, and brain circuitry. *Journal of the American Academy of Child and Adolescent Psychiatry* 53: 417–424.
67. Roth TL, Lubin FD, Funk AJ, et al. (2009) Lasting epigenetic influence of early-life adversity on the BDNF gene. *Biological Psychiatry* 65: 760–769.
68. Roth TL, Zoladz PR, Sweatt JD, et al. (2011) Epigenetic modification of hippocampal BDNF DNA in adult rats in an animal model of post-traumatic stress disorder. *Journal of Psychiatric Research* 45: 919–929.
69. Heim C, Shugart M, Craighead WE, et al. (2010) Neurobiological and psychiatric consequences of child abuse and neglect. *Developmental Psychobiology* 52: 671–690.
70. McGowan PO, Sasaki A, D'Alessio AC, et al. (2009) Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nature Neuroscience* 12: 342–348.
71. Conradt E, Lester BM, Appleton AA, et al. (2013) The roles of DNA methylation of NR3C1 and 11β-HSD2 and exposure to maternal mood disorder in utero on newborn neurobehavior. *Epigenetics* 8: 1321–1329.
72. Perroud N, Paoloni-Giacobino A, Prada P, et al. (2011) Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: A link with the severity and type of trauma. *Translational Psychiatry* 1: e59.
73. Serafini G, Pompili M, Elena Seretti M, et al. (2013) The role of inflammatory cytokines in suicidal behavior: A systematic review. *European Neuropsychopharmacology* 23(12): 1672–1686.
74. Ducasse D, Olié E, Guillaume S, et al. (2015) A meta-analysis of cytokines in suicidal behavior. *Brain Behavior Immunology* 46: 203–211.
75. Black C and Miller BJ (2015) Meta-analysis of cytokines and chemokines in suicidality: Distinguishing suicidal versus nonsuicidal patients. *Biological Psychiatry* 78: 28–37.
76. Poznanski E and Mokros H (1996) Children's Depression Rating Scale–Revised (CDRS-R). Los Angeles, CA: WPS.

77. Kaufman J, Birmaher B, Brent D, et al. (1997) Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry* 36(7): 980–988.
78. Shaffer D, Gould M, Brasic J, et al. (1985) A Children's Global Assessment Scale (CGAS) (for children 4–16 years of age). *Psychopharmacology Bulletin* 21: 747–748.
79. Beck AT, Ward CH, Mendelson M, et al. (1961) An inventory for measuring depression. *Archives of General Psychiatry* 4(6): 561–571.
80. Beck AT, Kovacs M and Weissman A (1979) Assessment of suicidal intention: The scale for suicide ideation. *Journal of Consulting and Clinical Psychology* 47: 343–352.
81. Asberg M, Montgomery SA, Perris C, et al. (1978) A comprehensive psychopathological rating scale. *Acta Psychiatrica Scandinavica Supplementum* 271: 5–27.
82. Stanley B, Traskman-Bendz L and Stanley M (1986) The suicide assessment scale: A scale evaluating change in suicidal behavior. *Psychopharmacology Bulletin* 22: 200–205.
83. Tyrer P, Owen RT and Cicchetti DV (1984) The brief scale for anxiety: A subdivision of the comprehensive psychopathological rating scale. *Journal of Neurology Neurosurgery and Psychiatry* 47: 970–975.
84. First M (1997) *Structured clinical interview for DSM-IV axis I disorders (SCID-I)*. Washington, DC: American Psychiatric Press.
85. First M (1997) *Structured clinical interview for DSM-IV axis II personality disorders (SCID-II)*. Washington, DC: American Psychiatric Press.
86. World Health Organization (WHO) (2002) The alcohol, smoking and substance involvement screening test (ASSIST): Development, reliability and feasibility. *Addiction* 97(9): 1183–1194.
87. Sheehan DV, Lecrubier Y, Sheehan KH, et al. (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry* 59 (Suppl. 20): 22–33.
88. Hamilton M (1960) A rating scale for depression. *Journal of Neurology Neurosurgery and Psychiatry* 23: 56–62.
89. Overall JE and Gorham DR (1962) The brief psychiatric rating scale. *Psychology Reports* 10: 799–812.
90. Weisman AD and Worden JW (1972) Risk-rescue rating in suicide assessment. *Archives of General Psychiatry* 26: 553–560.
91. Berman AL, Shepherd G and Silverman MM (2003) The LSARS-II: Lethality of suicide attempt rating scale-updated. *Suicide & Life-Threatening Behavior* 33: 261–276.
92. Smith K, Conroy RW and Ehler BD (1984) Lethality of suicide attempt rating scale. *Suicide & Life-Threatening Behavior* 14: 215–242.
93. Gabbay V, Klein RG, Guttman LE, et al. (2009) A preliminary study of cytokines in suicidal and non-suicidal adolescents with major depression. *Journal of Child and Adolescent Psychopharmacology* 19: 423–430.
94. Janelidze S, Mattei D, Westrin A, et al. (2011) Cytokine levels in the blood may distinguish suicide attempters from depressed patients. *Brain Behavior Immunology* 25: 335–339.
95. O'Donovan A, Rush G, Hoatam G, et al. (2013) Suicidal ideation is associated with elevated inflammation in patients with major depressive disorder. *Depression and Anxiety* 30: 307–314.
96. Lindqvist D, Janelidze S, Hagell P, et al. (2009) Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. *Biological Psychiatry* 66: 287–292.
97. Janelidze S, Suchankova P, Ekman A, et al. (2015) Low IL-8 is associated with anxiety in suicidal patients: Genetic variation and decreased protein levels. *Acta Psychiatrica Scandinavica* 131: 269–278.
98. Vargas HO, Nunes SO, Pizzo de Castro M, et al. (2013) Oxidative stress and lowered total antioxidant status are associated with a history of suicide attempts. *Journal of Affective Disorders* 150: 923–930.
99. Isung J, Mobarrez F, Nordström P, et al. (2012) Low plasma vascular endothelial growth factor (VEGF) associated with completed suicide. *World Journal of Biological Psychiatry* 13: 468–473.
100. Li Z, Qi D, Chen J, et al. (2013) Venlafaxine inhibits the upregulation of plasma tumor necrosis factor-alpha (TNF-alpha) in the Chinese patients with major depressive disorder: A prospective longitudinal study. *Psychoneuroendocrinology* 38: 107–114.
101. Nassberger L and Traskman-Bendz L (1993) Increased soluble interleukin-2 receptor concentrations in suicide attempters. *Acta Psychiatrica Scandinavica* 88: 48–52.
102. Mendlovic S, Mozes E, Eilat E, et al. (1999) Immune activation in non-treated suicidal major depression. *Immunology Letters* 67: 105–108.
103. Kim YK, Lee SW, Kim SH, et al. (2008) Differences in cytokines between non-suicidal patients and suicidal patients in major depression. *Progress in*

Neuropsychopharmacology & Biological Psychiatry 32: 356–361.

104. Lee HY and Kim YK (2010) Transforming growth factor-beta1 and major depressive disorder with and without attempted suicide: Preliminary study. *Psychiatry Research* 178: 92–96.
105. Lee KM and Kim YK (2006) The role of IL-12 and TGF-beta1 in the pathophysiology of major depressive disorder. *International Immunopharmacology* 6(8): 1298–1304.
106. Pandey GN, Rizavi HS, Ren X, et al. (2012) Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. *Journal of Psychiatric Research* 46: 57–63.
107. Boehm J, Fischer K and Bohnert M (2010) Putative role of TNF-alpha, interleukin-8 and ICAM-1 as indicators of an early inflammatory reaction after burn: A morphological and immunohistochemical study of lung tissue of fire victims. *Journal of Clinical Pathology* 63: 967–971.
108. Tonelli LH, Stiller J, Rujescu D, et al. (2008) Elevated cytokine expression in the orbitofrontal cortex of victims of suicide. *Acta Psychiatrica Scandinavica* 117: 198–206.