A Meta-Analysis of Cytokines in Major Depression

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Background: Major depression occurs in 4.4% to 20% of the general population. Studies suggest that major depression is accompanied by immune dysregulation and activation of the inflammatory response system (IRS). Our objective was to quantitatively summarize the data on concentrations of specific cytokines in patients diagnosed with a major depressive episode and controls.

Methods: We performed a meta-analysis of studies measuring cytokine concentration in patients with major depression, with a database search of the English literature (to August 2009) and a manual search of references.

Results: Twenty-four studies involving unstimulated measurements of cytokines in patients meeting DSM criteria for major depression were included in the meta-analysis; 13 for tumor necrosis factor (TNF)-α, 9 for interleukin (IL)-1β, 16 for IL-6, 5 for IL-4, 5 for IL-2, 4 for IL-8, 6 for IL-10, and 4 for interferon (IFN)-γ. There were significantly higher concentrations of TNF-α ($p < .00001$), weighted mean difference (WMD) (95% confidence interval) 3.97 pg/mL (2.24 to 5.71), in depressed subjects compared with control subjects (438 depressed/350 nondepressed). Also, IL-6 concentrations were significantly higher ($p < .00001$) in depressed subjects compared with control subjects (492 depressed/400 nondepressed) with an overall WMD of 1.78 pg/mL (1.23 to 2.33). There were no significant differences among depressed and nondepressed subjects for the other cytokines studied.

Conclusions: This meta-analysis reports significantly higher concentrations of the proinflammatory cytokines TNF-α and IL-6 in depressed subjects compared with control subjects. While both positive and negative results have been reported in individual studies, this meta-analytic result strengthens evidence that depression is accompanied by activation of the IRS.

Key Words: Anti-inflammatory cytokines, depression, meta-analysis, proinflammatory cytokine

Major depression is an important public health issue (1) with a lifetime prevalence of 4.4% to 20% in the general population (2). The DSM-IV (3) stipulates that at least five of nine criteria depressive symptoms must be present, including either sadness or anhedonia, for at least 2 weeks to diagnose a major depressive episode. Depressive symptoms may also include fatigue, feelings of worthlessness or guilt, lack of ability to concentrate, suicidal ideation, or significant changes in weight or sleep. The impact of depression on quality of life is comparable with or greater than that of chronic medical illness (4,5), depending on the severity of symptoms (5), and depression is considered disabling to psychosocial function (6).

The monoamine hypothesis is the most extensively studied etiologic theory of depression (7,8) and virtually all available antidepressants act, at least in part, by increasing monoaminergic transmission. However, meta-analyses suggest that these agents are effective for only one half to one third of patients suffering from depression (9–13) and they often produce side effects that can sometimes limit their usefulness (11,12,14). Those studies underscore the urgent need for alternative or corollary hypotheses to help guide the development of more effective or adjunctive treatment strategies.

Numerous studies have suggested that major depression is accompanied by immune dysregulation. Specifically, activation of the inflammatory response system (IRS) has been demonstrated by increased production of proinflammatory cytokines such as interleukin (IL)-1β, IL-2, IL-6, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, the soluble IL-6 receptor (IL-6R), and the IL-1 receptor antagonist (IL-1RA) (15–25). These findings may be clinically important because proinflammatory cytokines can contribute directly to the development of depressive symptoms (26). Proinflammatory cytokines have been shown to induce stress-reactive neuroendocrine and central neurotransmitter changes reminiscent of those in depression (26), and it has been demonstrated that immunotherapy with IFN-α can precipitate depression (27).

Although an association between IRS activation and depression has been documented in individual studies (17–26,28) of various cytokines, the association is not consistently significant in all studies or for all cytokines (29–31). Thus, a generalizable pattern of immune dysfunction in major depression remains to be defined. However, results from individual studies can be combined quantitatively using meta-analytical techniques to improve the strength of the evidence. Therefore, this study reports the results of a meta-analysis conducted to determine whether the concentrations of specific cytokines differ quantitatively between patients diagnosed with a major depressive episode and control subjects.

Methods and Materials

Only original studies that measured cytokine concentrations in depressed and nondepressed subjects were included in the meta-analysis. Studies were included if subjects met DSM-III-R or DSM-IV (3) criteria for major depression. Studies were included if they were published in English, if cytokine concentrations were measured in subjects free of major medical comorbidities (cancer, heart disease, etc.), if subjects were free of antidepressant medications for at least 1 week before the initiation of the study, if psychiatrically healthy subjects were used as control subjects, and if cytokine concentrations were measured in the unstimulated state and in the morning. Studies looking at stimulated levels of cytokines were excluded because they differ in

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Received Jun 9, 2009; revised Aug 31, 2009; accepted Sep 26, 2009.

0006-3223/10/$36.00
doi:10.1016/j.biopsych.2009.09.033

that they reflect the consequences of immune challenge as opposed to basal immune activity.

This analysis was performed according to Quality of Reporting of Meta-Analyses (QUORUM) guidelines for conducting a meta-analysis (32). We searched English language literature using MEDLINE, EMBASE, PsycINFO, Cochrane Database of Systematic Reviews, AMED, and CINAHL from June 1960 to August 2009 using the key words depression, cytokine, interferon, interleukin, TNF-α, IL-1β, IL-6, IL-4, IL-2, IL-8, IL-10, and IFN-γ. The reference lists of all the relevant studies were also searched for any additional trials.

Each article was separately examined by two independent raters and results were compared. Disagreements regarding inclusion were settled by consensus.

Two independent raters examined the Methods and Results sections of each relevant article, and data for mean (±SD) cytokine concentrations for each group of depressed and nondepressed subjects were extracted. We used Review Manager Version 5.0 (Cochrane Collaboration, Oxford, United Kingdom) for analysis. For our continuous outcomes data, a weighted mean difference and 95% confidence intervals (CIs) were calculated using a random effects model. This meta-analytic method includes both within-study variance and between-studies variation in the estimate of the uncertainty (confidence interval) around results. Unlike a fixed effects model, a random effects model assumes that the underlying true effects vary from one study to another. Random effects models will give wider confidence intervals than fixed effect models, if there is significant heterogeneity among the results of the included studies. Thus, a random effects model is more conservative and is chosen if significant heterogeneity is expected.

Heterogeneity was tested for all combined results by means of a Q statistic (calculated using a chi-square analysis), and inconsistency was calculated using an I^2 index to determine the impact of heterogeneity (33). The presence of significant heterogeneity suggests diversity in characteristics of the trials. Likely sources of heterogeneity, such as severity of illness, diagnosis, age, gender, setting, and type of assay, were investigated. Publication bias was assessed where there were five or more studies using funnel plots and rank correlation tests between effect size and sample size (34,35). Altman's (36) method of describing CIs was used when the difference between groups was not statistically significant.

Results

A total of 136 studies were identified for review. One hundred twelve studies did not meet inclusion criteria. Studies were

Table 1. Characteristics of Included Studies of Looking at Cytokine Concentrations in Depression

Study/Year	Cytokines Measured	*N* (D, ND)	Gender (% Male) (D, ND)	Age[a] (D, ND)	Depression Diagnosis (Scales)
Berk *et al.*, 1997 (29)	IL-6	28/21	36.3/NR	41.9/NR	DSM
Brambilla and Maggioni, 1998 (30)	TNF-α/IL-1β/IL-6	10/10	0/0	72 ± 4/71 ± 3	DSM
Brambilla *et al.*, 2004 (156)	TNF-α/IL-1β	11/11	81.8/72.7	12.2 ± 1.7/11.4 ± 2.4	DSM, Poznanski Rating Scale
Dhabhar *et al.*, 2009 (155)	IL-6, IL-10	12/11	41.7/45.5	38.4 ± 11/38 ± 13.3	DSM, HAM-D
Eller *et al.*, 2008 (157)	TNF-α/IL-8	100/45	35.0/42.2	23.1 ± 11.9/32.9 ± 14.1	DSM, MADRS
Hernandez *et al.*, 2008 (161)	IL-2/IFN-γ/IL-4/IL-10/IL-1β	31/22	29.0/31.2	32.0 ± 9.4/30.8 ± 6.3	DSM, HAM-D, BDI
Huang *et al.*, 2007 (158)	TNF-α/IL-1β/IL-10	42/40	28.6/37. 5	38 ± 8.2/31.4 ± 3.9	DSM, HAM-D
Jozuka *et al.*, 2003 (162)	IL-2	17/10	47.1/40.0	40.3 ± 15.3/39.9 ± 9.8	DSM, ZDS
Kagaya *et al.*, 2001 (143)	TNF-α/IL-1β/IL-6	12/12	75.0/75.0	31.1 ± 8.2/30.9 ± 7	DSM, HAM-D, POMS
Kubera *et al.*, 2000 (150)	IL-6/IL-10	9/10			DSM, HAM-D
Leo *et al.*, 2006 (144)	TNF-α/IL-1β/IL-6	46/46	43.5/41.3	34.9 ± 5.9/34.1 ± 5.2	DSM, HAM-D
Maes *et al.*, 1995 (151)	IL-6	61/38	59.0/55.3	36.6 ± 1.3/33.8 ± 1.5	DSM, HAM-D
Maes *et al.*, 1995 (152)	IL-6	13/28	53.8/64.3	35.2 ± 12.2/36.1 ± 4.9	DSM, HAM-D
Maes *et al.*, 1997 (17)	IL-6	35/15	54.3/66.7	50.3 ± 13.9/47.5 ± 15.0	DSM, HAM-D
Mikova *et al.*, 2001 (145)	TNF-α/IL-6/IL-8	28/15	17.9/46. 7	47.3 ± 11.3/42 ± 10.9	DSM, HAM-D
Myint *et al.*, 2005 (163)	IL-4/IFN-γ	18/3	32.5/32.5	40.7 ± 15.5/40.3 ± 13.1	DSM, HAM-D, BPRS
O'Brien *et al.*, 2007 (146)	TNF-α/IL-6/IL-8/IL-10	TNF-α, IL-6 28/24; IL-8, IL-10 28/68	32.1/41.6 (n = 24)	44.2 ± 13.2/35.6 ± 9 (n = 24)	DSM, HAM-D
Pavon *et al.*, 2006 (147)	TNF-α/IL-1β/IL-6/IL-4/IFN-γ/IL-2	33/33	15.2/15. 2	33.6 ± 10.2/32.3 ± 10.8	DSM, HAM-D
Pike and Irwin, 2006 (153)	IL-6	25/25	100/100	42.5 ± 9.2/42.7 ± 12	DSM, HAM-D
Simon *et al.*, 2008 (148)	TNF-α/IL-1β/IL-6/IL-4/IFN-γ/IL-2/IL-8/IL-10	49/49	59.2/57.1	41.7 ± 11.1/41.7 ± 11.3	DSM
Sluzewska *et al.*, 1996 (154)	IL-6	49/15	18.4/NR	42.3 ± 6.5/NR	DSM, HAM-D
Sutcigil *et al.*, 2007 (159)	TNF-α/IL-4/IL-2	23/25	52.2/52.0	34.8 ± 7.4/34.3 ± 7.8	DSM, HAM-D
Tuglu *et al.*, 2003 (160)	TNF-α	26/17	57.7/64.7	39.4 ± 14.6/37.1 ± 11.1	DSM, HAM-D, BDI
Yang *et al.*, 2007 (149)	TNF-α/IL-1β/IL-6	33/23	27.3/30. 4	42.1 ± 2.3/38.4 ± 1.8	DSM, HAM-D

BDI, Beck Depression Inventory; BPRS, Brief Psychiatric Rating Scale; D, depressed; DSM, Diagnostic and Statistical Manual of Mental Disorders; HAM-D, Hamilton Depression Rating Scale; IFN-γ, interferon γ; IL, interleukin; MADRS, Montgomery-Åsberg Depression Rating Scale; ND, nondepressed; NR, not reported; POMS, Profile of Mood States; TFN-α, tumor necrosis factor α; ZDS, Zung Depression Scale.

[a]Values reflect mean ± SD in each group.