

Antidepressant Activity of Anti-Cytokine Treatment: A Systematic Review and Meta-analysis of Clinical Trials of Chronic Inflammatory Conditions

Running Title: Antidepressant Activity of Anti-Cytokine Treatment

Nils Kappelmann, Bsc¹; Glyn Lewis, PhD²; Robert Dantzer, PhD³; Peter B Jones, PhD^{1,4†};

Golam M Khandaker, PhD^{1,4†}

† Equal contribution

¹ Department of Psychiatry, University of Cambridge, Cambridge, UK

² Division of Psychiatry, University College London, London, UK

³ Department of Symptom Research, University of Texas MD Anderson Cancer Centre, Houston, Texas, USA

⁴ Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK

Address for Correspondence: Dr Golam Khandaker, Department of Psychiatry, University of Cambridge, Box 189, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK. Tel: +44 1223 768510; Fax: +44 1223 336968; Email: gmk24@medschl.cam.ac.uk

Word count:

Abstract: 259

Body: 4238

Tables and Figures: 1 Table + 4 Figures + 7 online supplementary Figures

Abstract

Inflammatory cytokines are commonly elevated in acute depression and are associated with resistance to monoaminergic treatment. To examine the potential role of cytokines in the pathogenesis and treatment of depression, we carried out a systematic review and meta-analysis of antidepressant activity of anti-cytokine treatment using clinical trials of chronic inflammatory conditions where depressive symptoms were measured as a secondary outcome. Systematic search of the PubMed, EMBASE, PsycINFO, and Cochrane databases, search of reference lists and conference abstracts, followed by study selection process yielded 20 clinical trials. Random effect meta-analysis of seven randomised controlled trials (RCTs) involving 2370 participants showed a significant antidepressant effect of anti-cytokine treatment compared with placebo (standardized mean difference (SMD)=0.40, 95% confidence interval (CI), 0.22-0.59). Anti-TNF drugs were most commonly studied (five RCTs); SMD=0.33 (95% CI; 0.06-0.60). Separate meta-analyses of two RCTs of adjunctive treatment with anti-cytokine therapy and eight non-randomised and/or non-placebo studies yielded similar small-to-medium effect estimates favouring anti-cytokine therapy; SMD=0.19 (95% CI, 0.00-0.37) and 0.51 (95% CI, 0.34-0.67), respectively. Adalimumab, etanercept, infliximab and tocilizumab all showed statistically significant improvements in depressive symptoms. Meta-regression exploring predictors of response found that the antidepressant effect was associated with baseline symptom severity ($P=0.018$) but not with improvement in primary physical illness, sex, age or study duration. The findings indicate a potentially causal role for cytokines in depression and that cytokine modulators may be novel drugs for depression in chronically inflamed subjects. The field now requires RCTs of cytokine modulators using depression as the primary outcome in subjects with high inflammation who are free of other physical illnesses.

Keywords: Monoclonal Antibody; Cytokine Inhibitor; Non-Steroidal Anti-Inflammatory Drug; Adalimumab; Dupilumab; Etanercept; Infliximab; Tocilizumab; Ustekinumab; Inflammation; Cytokine; Immune System; Depression; Depressive Symptom; Randomised Controlled Trial; Treatment; Meta-Analysis; Systematic Review

Introduction

The association between the immune system and the brain may offer new mechanistic understanding and insights for novel therapies for depression. Cytokine-mediated communication between the immune system and the brain has been implicated in the pathogenesis of depression.¹⁻³ Major depression is common (one in four) after interferon treatment, a potent inducer of cytokines, in patients affected by hepatitis C virus.⁴ Experimental immuno-activation in healthy volunteers leads to depressive symptoms and reduced cognitive performance.^{5, 6} Meta-analyses of cross-sectional studies confirm elevated levels of circulating inflammatory cytokines in depressed patients,⁷⁻¹⁰ and longitudinal studies have demonstrated that elevated serum cytokine levels precede, so potentially cause depressive symptoms.^{11, 12} A dose-response relationship between serum concentration of interleukin 6 (IL-6) in childhood at 9 years and subsequent depressive symptoms in early-adulthood at 18 years has been reported in the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort.¹¹ A longitudinal association between circulating inflammatory markers and subsequent depressive symptoms has also been reported from the Whitehall II cohort.¹² Furthermore, activation of the inflammatory system is thought to underlie antidepressant resistance highlighting an involvement in treatment response.^{13, 14} Therefore, whether targeting inflammation, particularly inflammatory cytokines, could provide therapeutic benefit for patients with depression is a key question.

A meta-analysis of randomised controlled trials (RCTs)¹⁵ of non-steroidal anti-inflammatory drugs (NSAIDs), given as sole treatment or as adjunct to antidepressants, indicates that they **may be** more effective than placebo in treating depression (Cohen's $d=0.27$; 95% CI, 0.08-0.45),¹⁶ **although there are limitations of individual studies included such as attrition.** While these results point to an inflammatory component to depression, further examination of the

evidence regarding cytokine modulating drugs may help to elucidate the relevance of inflammation for pathogenesis and treatment of depression specifically. NSAIDs are broad-spectrum anti-inflammatory agents that also act on other targets, such as glucocorticoid receptors.¹⁷ These receptors are, themselves, relevant for depression pathophysiology,¹⁸ so the extent to which the antidepressant effect of NSAIDs is due solely to anti-inflammatory action is unclear. Some NSAIDs such as cyclooxygenase-2 inhibitors increase risk of cardiovascular disease,¹⁹ a known comorbidity for depression, so their use in depression may be problematic. Besides, many trials of anti-inflammatory drugs for depression are based on people with chronic physical illness¹⁶ but it is unclear whether the improvement in depression is due to the improvement in physical illness.

Cytokine modulators, which include monoclonal antibodies and cytokine inhibitors, constitute a more pure anti-inflammatory class because they target specific cytokine pathways. Recently, a proof-of-concept RCT of infliximab, a tumour necrosis factor alpha (TNF- α) specific monoclonal antibody, has reported improvements in patients with treatment resistant depression characterized by high inflammation at baseline.²⁰ Supported by a large number of RCTs, cytokine modulators are well established treatments for chronic inflammatory conditions such as rheumatoid arthritis (RA)²¹ and psoriasis.²² Many of these clinical trials have also reported on secondary psychosocial outcome measures including **depressive symptoms** which could be utilised to address important questions regarding potential usefulness of anti-cytokine treatment for depression. In addition to quantifying the antidepressant effect of anti-cytokine treatment, examination of the relationship between the improvement in **depressive symptoms** and that in physical symptoms could elucidate the role of inflammation in depression specifically. Previous RCTs indicate baseline severity of

depression moderates the antidepressant effects of monoaminergic drugs²³ and psychotherapy²⁴; it not clear whether this is also the case for anti-cytokine treatment.

We report a systematic review and meta-analysis of secondary data from clinical trials of anti-cytokine treatment in chronic inflammatory conditions to address the following key outstanding questions: (1) does blocking specific inflammatory cytokine pathways lead to improvement in **depressive symptoms**; (2) what is the relationship between the antidepressant effect and the improvement in physical illness; (3) is the antidepressant effect related to baseline severity of depressive symptoms; (4) is there any sex or age difference of the antidepressant effect. Answers to these questions would provide important clues on whether inflammatory cytokines play a causal role in depression, and whether cytokine modulators may be useful for treating depression.

Materials and Methods

Search strategy and study selection

A systematic search of the PubMed, Embase, PsycINFO, and Cochrane databases was carried out for all clinical trials of cytokine modulators involving human subjects published in the English language until 5th April 2016, where depression or **depressive symptoms** were reported as an outcome. The search terms included indexing terms as well as wildcards to maximize return: “(monoclonal antibod* OR cytokine inhibitor OR tocilizumab OR infliximab OR adalimumab OR ustekinumab OR etanercept OR dupilumab) AND (depression OR depressive symptom)”. We also searched reference lists of retrieved articles and conference abstracts, and wrote to key authors in the field for unpublished data.

Clinical trials of specific cytokine inhibitors or monoclonal antibodies against specific inflammatory cytokines that measured depressive symptoms using a recognised tool were included. In order to obtain a comprehensive overview of the literature, we included all clinical trial designs, i.e. RCTs, double blind or open label, as well as non-randomised studies (analysed separately). Studies that examined cytokine modulators as an adjunct to interferon (INF) therapy, used monoclonal antibodies as a method for detecting leukocyte subtypes, or examined monoclonal antibodies against targets other than an inflammatory cytokine (e.g. vascular growth factor, adhesion molecule) were excluded.²⁵ The literature search and study selection were carried out by NK and GMK; any differences were resolved by discussion.

Data extraction and statistical analysis

Data were extracted from published articles or obtained by directly contacting the authors if relevant data were not reported. When authors could not be reached but data were available in the paper in graph format (two RCTs),^{26, 27} values were extracted using software that has been shown to be a reliable method of data extraction for meta-analyses.²⁸ RCTs were quality assessed using the CONSORT criteria;²⁹ scores reflect the percentage of CONSORT items the study adhered to. We aligned depression scales so higher scores reflect higher symptom severity by multiplying scores from reversed scales by -1. For studies that included multiple intervention arms based on different dosages of the same drug, we pooled means and standard deviations of these groups to calculate a single outcome measure. Here, the pooled standard deviation (sd_{pooled}) equalled the square root of $(sd_1^2 * (n_1 - 1) + sd_2^2 * (n_2 - 1)) / ((n_1 - 1) + (n_2 - 1))$. Effect sizes were calculated as standardised mean difference (SMD) for continuous outcomes according to the formula $(\bar{x}_1 - \bar{x}_2) / sd_{pooled}$. For binary outcomes odds ratios (ORs) were created according to the formula $(Outcome_1Group_1 * Outcome_2Group_2) /$

($\text{Outcome}_2\text{Group}_1 * \text{Outcome}_1\text{Group}_2$). Then ORs were transformed to SMD by dividing the natural logarithm of the ORs by 1.81.³⁰

Based on study methodology, three types of studies were combined separately using random effect meta-analysis: RCTs of anti-cytokine drug vs. placebo; RCTs of adjunctive treatment with anti-cytokine therapy (anti-cytokine drug *plus* active treatment vs. active treatment); and other trials (non-randomised and/or non-placebo studies). For RCTs effect estimates were calculated as SMD using depression severity scores in treatment and placebo groups at the end of trial. SMD is an appropriate measure of effect estimate when studies assess the same variable (e.g. depressive symptoms) but measure it in a variety of ways.³¹ In addition, we calculated SMD using change in depression severity score from baseline to end of trial in each group to examine the robustness of original results (sensitivity analysis). Sensitivity analyses were also carried out after excluding specific RCTs from meta-analysis. For other trials, SMD was calculated as difference in depression severity score from baseline to end of trial since no control group was present. All studies were weighted using an inverse-variance method so studies with larger samples were given higher weight. When possible, pooled effect estimates were calculated for specific drugs. Heterogeneity between studies was investigated by calculating the Cochrane's heterogeneity statistic Q and the I^2 statistic that represents the fraction of variation between studies attributable to heterogeneity.³² Publication bias was assessed for each group of studies by visual inspection of funnel plots including Egger's test,³³ and the trim and fill method.³⁴ We analysed the RCTs of adjunctive treatment with anti-cytokine therapy separately because these studies compared combination of anti-cytokine drug and a disease-modifying anti-rheumatic drug (DMARD) with DMARD alone. One RCT³⁵ administered adalimumab to all participants for four weeks before randomising them to placebo or adalimumab for subsequent 52 weeks, so we also included

data from the first four weeks in the meta-analysis of “other trials”. Data from two studies³⁶,³⁷ that randomised individuals to different dosage regimens of the same drug but lacked a placebo group, and a non-randomised study³⁸ were also included in this category.

All secondary analyses were based on placebo-controlled RCTs only as they represent the highest quality of scientific evidence of efficacy. Meta-regressions were performed to examine the relationship between the effect estimates for depression and (1) the effect estimates for primary physical outcome; (2) baseline severity of **depressive symptoms**; (3) sex (percentage of male participants in each sample); and (4) mean age of sample. We quantified baseline depression **symptom severity** in a standardised manner rather than simply using mean scores because the studies used different scales to measure depression. We identified general population distributions for each scale³⁹⁻⁴³ that were used to calculate effect sizes (SMD) of baseline **symptom severity** for the sample compared to the general population. All analyses were performed in *R* using the *metaphor* package for meta-analysis and meta-regression;⁴⁴ **analysis codes are available on request.**

Results

The literature search retrieved 350 potentially relevant articles of which 20 studies were finally included in the review (see Figure 1 for a PRISMA diagram of literature search). Of the included studies, seven were RCTs of anti-cytokine drug vs. placebo, three were RCTs of adjunctive treatment with anti-cytokine therapy, and 10 were other study designs such as non-randomised and/or non-placebo studies (Table 1).

--- Insert Figure 1 here ---

--- Insert Table 1 here ---

Meta-analysis of RCTs of anti-cytokine drug vs. placebo

Meta-analysis of seven randomised, double-blind, placebo-controlled trials,^{20, 26, 27, 35, 45-47} involving 1309 subjects treated with anti-cytokine drugs and 1061 subjects treated with placebo, showed significant improvement in depressive symptoms with anti-cytokine treatment compared to placebo; SMD=0.40 (95% confidence interval (CI), 0.22-0.59) (Figure 2a). There was evidence of significant heterogeneity among studies ($P<0.001$; $I^2=73\%$). Anti-TNF drugs were most commonly studied (five RCTs),^{20, 26, 27, 35, 46} which as a group showed significant antidepressant effect; SMD=0.33; 95% CI, 0.06-0.60 (Figure 3). There was also evidence of significant heterogeneity among these studies ($P=0.02$; $I^2=75\%$). Regarding specific drugs, based on two trials each, the effect estimate for adalimumab^{35, 46} (SMD=0.39; 95% CI, 0.05-0.72) and that for etanercept^{26, 27} (SMD=0.45; 95% CI, 0.07-0.83) were similar (Figure 2a). There was no evidence of significant heterogeneity between the adalimumab trials ($P=0.134$; $I^2=55\%$) but there was evidence of heterogeneity among the etanercept trials ($P=0.05$, $I^2=73\%$).

Sensitivity analysis of seven RCTs,^{20, 26, 27, 35, 45-47} of anti-cytokine drugs vs. placebo based on change in depression severity scores from baseline to end of trial yielded very similar results to that of the original analysis; SMD=0.37 (95% CI; 0.18-0.57) (see online supplementary Figure 1). However, evidence for heterogeneity remained ($P<0.001$; $I^2=76\%$).

--- Insert Figure 2 here ---

--- Insert Figure 3 here ---

Meta-analysis of RCTs of adjunctive treatment with anti-cytokine therapy

Of three trials⁴⁸⁻⁵⁰ that used anti-cytokine drugs as adjunctive treatment, two provided enough data for meta-analysis (Figure 2b).^{49, 50} Both of these studies compared combination of etanercept and a DMARD (n=544) with DMARD alone (n=405). Meta-analysis showed a small effect of etanercept plus DMARD on depressive symptoms compared to DMARD alone (SMD=0.19; 95% CI, 0.00-0.37). There was no evidence of heterogeneity between studies ($P=0.158$; $I^2=49\%$).

Meta-analysis of other trials

Out of 10 non-randomised and/or non-placebo studies,^{36-38, 51-57} eight provided enough data for meta-analysis involving 1744 patients with data at baseline and follow-up (Figure 2c).^{35, 36, 38, 51-55} Meta-analysis of these studies suggested significant improvement in depressive symptoms following anti-cytokine treatment (SMD=0.51; 95% CI, 0.34-0.67). There was evidence of significant heterogeneity among these studies ($P < 0.001$; $I^2 = 73\%$). Anti-TNF drugs were most commonly studied (six studies), which as a group showed significant anti-depressant effect (SMD=0.58; 95% CI, 0.39-0.77) (see online supplementary Figure 2). However, there was evidence for significant heterogeneity among these studies ($P=0.002$; $I^2 = 67\%$). Regarding specific drugs, adalimumab, infliximab and tocilizumab all showed statistically significant improvements in depressive symptoms. Meta-analytic effect estimates for adalimumab: SMD=0.67 (95% CI, 0.47-0.87); infliximab: SMD=0.66 (95% CI, 0.14-1.18); and tocilizumab: SMD=0.31 (95% CI, 0.20-0.42). There was no evidence of significant heterogeneity in any of these meta-analyses (all $P>0.05$).

Association with improvement in physical illness

Meta regression of six RCTs^{26, 27, 35, 45-47} found no evidence for an association between improvement in depressive symptoms and that in primary physical illness outcome measure at the end of trial ($slope=0.37$; $SE=0.28$; $P=0.182$) (Figure 4). The study by Raison *et al.* was excluded from this analysis because in this trial depression was the primary outcome so no physical illness was studied.²⁰

--- Insert Figure 4 here ---

Association with depression symptom severity at baseline

Meta-regression of seven RCTs^{20, 26, 27, 35, 45-47} showed an association between antidepressant effect of anti-cytokine treatment and baseline severity of depressive symptoms ($slope=-0.12$; $SE=0.05$; $P=0.018$). However, the association became non-significant after excluding the RCT by Raison *et al.*²⁰ ($slope=-0.05$; $SE=0.12$; $P=0.662$). We explored the association by excluding the RCT by Raison *et al.*²⁰ because baseline depression severity was much higher in this study (SMD of baseline depression 6.36) compared with the other RCTs (0.08-1.91).

Association with sex and age

There was no strong evidence for a sex difference in the antidepressant effect of anti-cytokine treatment as the association between improvements in depressive symptoms and the percentage of male subjects in the sample, based on meta-regression of seven RCTs,^{20, 26, 27, 35, 45-47} did not reach significance ($slope=1.29$; $SE=0.66$; $P=0.051$). Re-analysis after excluding the study by Raison *et al.*,²⁰ an outlier in which only 33% of subjects were male, attenuated the association further ($slope=0.66$; $SE=0.71$; $P=0.355$). Similarly there was no association

between SMD for depressive symptoms and mean age of sample ($slope=0.008$; $SE=0.028$; $P=0.788$).

Association with study duration

Duration of follow-up in the RCTs of anti-cytokine drug vs. placebo was similar (12-16 weeks) except the study by Loftus *et al* (Table 1). Meta-regression of seven RCTs^{20, 26, 27, 35, 45-47} showed no association between the antidepressant effect of anti-cytokine treatment and study duration ($slope=-0.004$; $SE=0.007$; $P=0.52$).

Sensitivity analyses

Sensitivity analysis of RCTs^{20, 35, 45-47} excluding two studies by Tyring *et al*^{26, 27} from which data were extracted using software did not change results substantially; $SMD=0.37$ (95% CI; 0.11-0.63) (see online supplementary Figure 3). However, evidence for significant heterogeneity remained ($P=0.003$; $I^2=79\%$). Unlike the other RCTs, the trial by Raison *et al*²⁰ was based on cases of treatment resistant depression without any significant physical comorbidity. Meta-analysis of RCTs^{26, 27, 35, 45-47} excluding this trial yielded a slightly larger effect estimate; $SMD=0.46$ (95% CI; 0.30-0.61) (see online supplementary Figure 4). However, there was evidence for significant heterogeneity among these studies ($P=0.016$; $I^2=61\%$). The RCT by Loftus *et al*³⁵ was an outlier in terms of follow-up length (see Table 1). Meta-analysis excluding this RCT^{20, 26, 27, 45-47} did not alter results greatly; $SMD=0.43$ (95% CI; 0.21-0.65) (see online supplementary Figure 5). However, evidence for significant heterogeneity remained ($P=0.002$; $I^2=76\%$).

Assessment of publication bias

Visual inspection of funnel plot of effect estimates from seven RCTs suggested that there was no evidence of publication bias (see online supplementary Figure 6), which was in line with a non-significant Egger's test for funnel plot asymmetry ($P>0.05$). Similarly, trim and fill analyses did not show any evidence of funnel plot asymmetry for RCTs. There were too few studies to allow assessment of publication bias among RCTs of adjunctive treatment with anti-cytokine therapy. For the other trials (non-randomised, non-placebo) Egger's test for funnel plot asymmetry ($P>0.05$) and visual inspection of the funnel plot did not suggest any evidence for publication bias (see online supplementary Figure 7). However, the trim and fill method indicated presence of funnel plot asymmetry, and that additional four studies would be needed to reach symmetry leading to slight attenuation of effect size (trim and fill SMD = 0.36; 95% CI, 0.18-0.55). It is known that the trim and fill method can underestimate effect estimates when there is significant heterogeneity among studies;⁵⁸ indeed, after restricting the analysis to anti-TNF studies heterogeneity decreased and there was no longer any evidence of funnel plot asymmetry ($P=0.50$).

Discussion

Findings from this large systematic review of 20 studies including meta-analyses of 16 studies totalling 5,063 participants indicate that anti-cytokine treatment improves depressive symptoms. We observed significant results favouring cytokine modulators over respective control groups with effect estimates of 0.40 for RCTs of anti-cytokine treatment vs. placebo, 0.19 for RCTs of adjunctive treatment with anti-cytokine therapy, and 0.51 for other (non-randomised and/or non-placebo) studies. Regarding predictors of response, additional analyses based on RCTs indicated that the antidepressant effect was associated with severity of depressive symptoms at baseline, but not with improvement in physical illness (primary

outcome under investigation in all but one RCT), sex and age of participants, or study duration. Sensitivity analyses using a different method to calculate SMD or exclusion of specific RCTs did not alter results substantially suggesting that the findings are robust. The results provide important clues regarding the role of inflammatory cytokines in depression and the potential for cytokine modulators as treatments for depression. Anti-cytokine drugs seem to offer treatment effects in the range of small to moderate effect sizes which is comparable to estimates observed for common antidepressants.²³ The results are in line with a previous meta-analysis of NSAIDs which included three RCTs of cytokine inhibitors.¹⁶ The results are also consistent with a recent meta-analysis of anti-TNF treatment in people with chronic physical illness that reported improvements in depression and anxiety symptoms.⁵⁹ However, based on a meta-analysis of seven RCTs the current study provides a robust, statistically significant effect estimate favouring anti-cytokine treatment for depression. In addition to the randomised, double-blind, placebo-controlled clinical trials (gold standard), we have examined RCTs of adjunctive treatment with anti-cytokine therapy, and non-randomised studies offering a comprehensive update of the literature.

Studies included in this review except one by Raison *et al*²⁰ report continuous measures of depression, i.e. symptom severity scores, not a categorical diagnosis of depression. To calculate effect size we have used depression severity scores for treatment and placebo groups at the end of trial for all RCTs including one by Raison *et al*. We also used change in depression scores from baseline to end of trial. The lack of an association between the improvement in depressive symptoms and that in primary physical illness points to a causal role for inflammatory cytokines in depression, suggesting that the mood improvement is not simply an artefact of feeling physically better after anti-cytokine treatment. Examination of the time course of effect in individual studies may provide some clues regarding the

underlying mechanism of antidepressant effect of anti-cytokine treatment. The RCT by Tyring *et al.*²⁷ reported scores for fatigue and depression during the course of 12-week treatment with etanercept vs. placebo for psoriasis. Compared with placebo, etanercept led to improvements in fatigue by two weeks into the study and in depressive symptoms by week four. In this study improvement in depressive symptoms was associated with improvement in fatigue but not (strongly) with improvement in psoriasis, which is in line with our meta-regression finding. Neurovegetative symptoms such as fatigue which develop rapidly following immune activation in humans are attributed to actions of inflammatory cytokines on the brain.^{60, 61} Therefore, it is possible that the antidepressant effect of anti-cytokine treatment is mediated by improvements in cytokine-induced neurovegetative symptoms. This hypothesis needs testing in future studies.

In future, RCTs of anti-cytokine treatment using depression as the primary outcome in subjects with high inflammation who are free of other physical illnesses are needed. While further studies are currently underway (e.g. NCT02363738 and NCT02473289), results from the RCT by Raison *et al.* included in this meta-analysis showed beneficial effects of infliximab for treatment resistant depression (TRD) cases only in those with elevated serum CRP levels at baseline.²⁰ TRD cases with elevated inflammatory marker levels may be ideal candidates for RCTs of cytokine modulators for a number of reasons. About a third of all depressed patients are antidepressant resistant⁶² and about a third of all depressed patients have elevated serum CRP (>3mg/L).⁶³ This may not be a coincidence. Indeed, activation of the inflammatory system as reflected by elevated serum inflammatory marker concentrations predicts poor antidepressant response,^{13, 14} and treatment resistant patients continue to show elevated cytokine levels.^{64, 65} Inflammation and consequent activation of the tryptophan metabolising enzyme indoleamine 2,3-dioxygenase (IDO) is thought to underlie persistent

symptoms despite antidepressant therapy in depressed patients who are 'inflamed'.⁶⁶ Inflammatory cytokines such as interferon- γ , TNF- α and IL-6 can induce IDO.^{67,68} In mice, blocking TNF- α with etanercept⁶⁷ or IL-6 with a monoclonal antibody⁶⁹ have been reported to prevent depression-like behaviour following exposures to an inflammatory stimulus or stress. **Therefore, cytokine modulating therapy is likely to be beneficial for a subset of depressed patients, specifically those with evidence of inflammation.**

Regarding specific types of studies, meta-analysis of two RCTs of anti-cytokine drugs as adjuncts to DMARD treatment showed a smaller effect size than that of the placebo-controlled randomised trials, which might be due to potential antidepressant effects of drugs used as comparison treatment. On the other hand, the pooled effect size for the non-randomised and/or non-placebo studies was larger than that for RCTs probably because of the lack of a comparison group to account for placebo effect. The association between baseline severity of **depressive symptoms** and response to anti-cytokine treatment was markedly reduced after excluding an outlier although an association between initial severity and antidepressant response is well known.²³ This is possibly because depression severity was relatively low in all of the RCTs except the one by Raison *et al.* which included cases of TRD.²⁰ **It is well known that baseline symptom severity is positively correlated with antidepressant treatment effect, so demonstration of a beneficial effect of anti-cytokine treatment in samples with relatively low depression scores indicates strong anti-depressant properties of these drugs.** There was no evidence for an association between antidepressant effect of cytokine modulators and sex or age of participants. Similar to depression, autoimmune chronic inflammatory conditions such as RA are more common in women than men (3:1),⁷⁰ but sex does not influence response to anti-TNF therapy in patients with established RA⁷¹ which is in line with our findings. A possible explanation for the lack of an

association with age could be limited variability in age among the included studies (<10 years).

Strengths of the systematic review presented here include a relatively large number of studies including RCTs which were quality assessed. The literature search was comprehensive, as supported by a lack of evidence for publication bias for most analyses. Inclusion of different trial methodologies allowed meta-analyses of two types of RCTs and non-randomised studies. The focus on a specific type of anti-inflammatory drug (i.e. cytokine modulators) helped to demonstrate the relevance of inflammation, particularly inflammatory cytokines, for the pathogenesis and treatment of depression. A potential limitation is the use of data extracted from published graphs due to lack of response from authors of two studies.^{26, 27}

However, the software used to extract data has been reported to be a reliable method for data extraction for meta-analysis,²⁸ so any variation from original data would be too small to have any meaningful impact on the pooled effect estimate. Because a physical illness was the primary outcome in all but one studies included in this review, we were not able to comment on potential side effects of cytokine-modulating treatment in depressed individuals specifically. Administration of monoclonal antibodies carries the risk of immune reactions such as acute anaphylaxis as well as various target-specific adverse effects including increased risk of infections, cancer and autoimmune disease.⁷² Infliximab and placebo groups in the study by Raison *et al.* were similar in terms of adverse events (except increased urinary leukocyte esterase in the placebo group) and no serious side effects were observed in either group.²⁰ Nevertheless, further studies regarding safety and tolerability of cytokine modulators in depressed individuals are needed. There was evidence for significant heterogeneity in the meta-analysis of RCTs and that of other trials. Heterogeneity is likely to be driven by heterogeneity of effect size because all studies included in these analyses except one showed

effect in the same direction, i.e. anti-cytokine treatment improves depressive symptoms (see Figures 2a, 2c). Heterogeneity was reduced when studies were grouped by specific monoclonal antibodies. For example, there was no evidence of heterogeneity among studies of adalimumab, infliximab and tocilizumab. However, sensitivity analyses after excluding specific RCTs did not reduce heterogeneity significantly.

In conclusion, this systematic review and meta-analysis provides an up-to-date summary of the existing literature on antidepressant effect of anti-cytokine treatment. The findings show robust improvements in depressive symptoms after anti-cytokine therapy (monoclonal antibody or cytokine inhibitor) with a small-to-moderate size effect. These results suggest inflammatory cytokines may play a key role in the pathogenesis of depression and that anti-cytokine drugs may be effective for some patients with depression, particularly treatment resistant cases characterised by increased inflammation. The field now needs RCTs of anti-cytokine treatment using such patients, which would pave the way for novel, effective and personalised treatment for depression and could reduce the burden presented by such a serious and multifactorial illness.

Acknowledgments

GMK is supported by a Clinical Lecturer Starter Grant from the Academy of Medical Sciences, UK (grant no. 80354) and a Gosling Fellowship from the Royal College of Psychiatrists, UK (2015). GMK also received funding support from the Wellcome Trust 094790/Z/10/Z). PBJ acknowledges grant support from the Wellcome Trust (095844/Z/11/Z & 088869/Z/09/Z) and NIHR (RP-PG-0606-1335, Cambridge Biomedical Research Centre and CLAHRC East of England). RD has received grants from the National Institute of Neurological Diseases and Stroke of the National Institutes of Health (grants R01 NS073939; R01 NS074999). The authors would like to thank the following individuals for supplying additional data for meta-analysis: Dr Daphne Guh, Center for Health Evaluation and Outcome Sciences, Canada; Dr Sara Berkö, BiogenIdec Sweden AB, Sweden; Dr Anders Svenningsson, Umeå University and University Hospital of Northern Sweden, Sweden; Dr Eric Simpson, University of Rochester Medical Center, USA; Dr Catherine Au, Regeneron Pharmaceuticals, USA; Prof Laure Gossec, Pierre and Marie Curie University, France; Dr Tina Bhutani, University of California San Francisco, USA. The authors would also like to thank Dr Valter Silva, Federal University of São Paulo, Brazil for his correspondence regarding data extraction methodology, and Dr Jan Stochl, University of Cambridge, UK for helpful comments on an earlier version of this manuscript.

Conflict of Interest

The authors have no competing financial interests in relation to the work described. PBJ received an honorarium that he donated to his department, from Roche (UK) for taking part in an advisory board to advise on education about schizophrenia for psychiatrists. RD received consulting fee and honorarium from Ironwood Pharma (USA) and Pfizer (France).

References

1. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature reviews Neuroscience* 2008; **9**(1): 46-56.
2. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol* 2006; **27**(1): 24-31.
3. Maes M. Evidence for an immune response in major depression: a review and hypothesis. *Progress in neuro-psychopharmacology & biological psychiatry* 1995; **19**(1): 11-38.
4. Udina M, Castellvi P, Moreno-Espana J, Navines R, Valdes M, Fornis X *et al.* Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. *J Clin Psychiatry* 2012; **73**(8): 1128-1138.
5. Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A *et al.* Cytokine-associated emotional and cognitive disturbances in humans. *Archives of general psychiatry* 2001; **58**(5): 445-452.
6. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. *Biological psychiatry* 2009; **66**(5): 407-414.

7. Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. *Molecular psychiatry* 2016.
8. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosomatic medicine* 2009; **71**(2): 171-186.
9. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK *et al.* A meta-analysis of cytokines in major depression. *Biological psychiatry* 2010; **67**(5): 446-457.
10. Haapakoski R, Mathieu J, Ebmeier KP, Alenius H, Kivimaki M. Cumulative meta-analysis of interleukins 6 and 1beta, tumour necrosis factor alpha and C-reactive protein in patients with major depressive disorder. *Brain, behavior, and immunity* 2015; **49**: 206-215.
11. Khandaker GM, Pearson RM, Zammit S, Lewis G, Jones PB. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. *JAMA psychiatry* 2014; **71**(10): 1121-1128.
12. Gimeno D, Kivimaki M, Brunner EJ, Elovainio M, De Vogli R, Steptoe A *et al.* Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. *Psychological medicine* 2009; **39**(3): 413-423.

13. Carvalho LA, Torre JP, Papadopoulos AS, Poon L, Juruena MF, Markopoulou K *et al.* Lack of clinical therapeutic benefit of antidepressants is associated overall activation of the inflammatory system. *Journal of affective disorders* 2013; **148**(1): 136-140.
14. Yoshimura R, Hori H, Ikenouchi-Sugita A, Umene-Nakano W, Ueda N, Nakamura J. Higher plasma interleukin-6 (IL-6) level is associated with SSRI- or SNRI-refractory depression. *Progress in neuro-psychopharmacology & biological psychiatry* 2009; **33**(4): 722-726.
15. Muller N, Schwarz MJ, Dehning S, Douhe A, Cerovecki A, Goldstein-Muller B *et al.* The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. *Molecular psychiatry* 2006; **11**(7): 680-684.
16. Kohler O, Benros ME, Nordentoft M, Farkouh ME, Iyengar RL, Mors O *et al.* Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA psychiatry* 2014; **71**(12): 1381-1391.
17. Hu F, Wang X, Pace TW, Wu H, Miller AH. Inhibition of COX-2 by celecoxib enhances glucocorticoid receptor function. *Molecular psychiatry* 2005; **10**(5): 426-428.

18. Pariante CM, Miller AH. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biological psychiatry* 2001; **49**(5): 391-404.
19. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA : the journal of the American Medical Association* 2001; **286**(8): 954-959.
20. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF *et al.* A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA psychiatry* 2013; **70**(1): 31-41.
21. Aaltonen KJ, Virkki LM, Malmivaara A, Konttinen YT, Nordstrom DC, Blom M. Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis. *PloS one* 2012; **7**(1): e30275.
22. Reich K, Burden AD, Eaton JN, Hawkins NS. Efficacy of biologics in the treatment of moderate to severe psoriasis: a network meta-analysis of randomized controlled trials. *The British journal of dermatology* 2012; **166**(1): 179-188.
23. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS medicine* 2008; **5**(2): e45.

24. Kessler D, Lewis G, Kaur S, Wiles N, King M, Weich S *et al.* Therapist-delivered Internet psychotherapy for depression in primary care: a randomised controlled trial. *Lancet* 2009; **374**(9690): 628-634.
25. Svenningsson A, Falk E, Celius EG, Fuchs S, Schreiber K, Berko S *et al.* Natalizumab treatment reduces fatigue in multiple sclerosis. Results from the TYNERGY trial; a study in the real life setting. *PloS one* 2013; **8**(3): e58643.
26. Tying S, Bagel J, Lynde C, Klekotka P, Thompson EH, Gandra SR *et al.* Patient-reported outcomes in moderate-to-severe plaque psoriasis with scalp involvement: results from a randomized, double-blind, placebo-controlled study of etanercept. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2013; **27**(1): 125-128.
27. Tying S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A *et al.* Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet* 2006; **367**(9504): 29-35.
28. Jelacic Kadic A, Vucic K, Dosenovic S, Sapunar D, Puljak L. Extracting data from figures with software was faster, with higher interrater reliability than manual extraction. *Journal of clinical epidemiology* 2016; **74**: 119-123.
29. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ *et al.* CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *Bmj* 2010; **340**: c869.

30. Chinn S. A simple method for converting an odds ratio to effect size for use in meta-analysis. *Statistics in medicine* 2000; **19**(22): 3127-3131.
31. Egger M, Smith DG, Altman DG. *Systematic Reviews in Health Care: Meta-Analysis in Context*. BMJ: London, 2001.
32. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine* 2002; **21**(11): 1539-1558.
33. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj* 1997; **315**(7109): 629-634.
34. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; **56**(2): 455-463.
35. Loftus EV, Feagan BG, Colombel JF, Rubin DT, Wu EQ, Yu AP *et al*. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. *The American journal of gastroenterology* 2008; **103**(12): 3132-3141.
36. Gniadecki R, Robertson D, Molta CT, Freundlich B, Pedersen R, Li W *et al*. Self-reported health outcomes in patients with psoriasis and psoriatic arthritis randomized to two etanercept regimens. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2012; **26**(11): 1436-1443.

37. Dauden E, Griffiths CE, Ortonne JP, Kragballe K, Molta CT, Robertson D *et al.* Improvements in patient-reported outcomes in moderate-to-severe psoriasis patients receiving continuous or paused etanercept treatment over 54 weeks: the CRYSTEL study. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2009; **23**(12): 1374-1382.
38. Minderhoud IM, Samsom M, Oldenburg B. Crohn's disease, fatigue, and infliximab: is there a role for cytokines in the pathogenesis of fatigue? *World journal of gastroenterology* 2007; **13**(14): 2089-2093.
39. Hinz A, Braehler E. Normative values for the hospital anxiety and depression scale (HADS) in the general German population. *Journal of psychosomatic research* 2011; **71**(2): 74-78.
40. Zimmerman M, Chelminski I, Posternak M. A review of studies of the Hamilton depression rating scale in healthy controls: implications for the definition of remission in treatment studies of depression. *The Journal of nervous and mental disease* 2004; **192**(9): 595-601.
41. Knight RG, Waal-Manning HJ, Spears GF. Some norms and reliability data for the State--Trait Anxiety Inventory and the Zung Self-Rating Depression scale. *The British journal of clinical psychology / the British Psychological Society* 1983; **22** (Pt 4): 245-249.

42. Jylha P, Isometsa E. Temperament, character and symptoms of anxiety and depression in the general population. *European psychiatry : the journal of the Association of European Psychiatrists* 2006; **21**(6): 389-395.
43. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S *et al.* The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *Journal of clinical epidemiology* 2010; **63**(11): 1179-1194.
44. Viechtbauer W. Conducting meta-analysis in R with the metafor package. *Journal of Statistical Software* 2010; **36**(1-48).
45. Simpson E, Worm M, Soong W, Blauvelt A, Eckert L, Wu R *et al.* Dupilumab Improves Patient-Reported Outcomes (PROs) in a Phase 2 Study in Adults with Moderate-to-Severe Atopic Dermatitis. *The Journal of Allergy and Clinical Immunology* 2015; **135**(2 suppl): AB167.
46. Menter A, Augustin M, Signorovitch J, Yu AP, Wu EQ, Gupta SR *et al.* The effect of adalimumab on reducing depression symptoms in patients with moderate to severe psoriasis: a randomized clinical trial. *Journal of the American Academy of Dermatology* 2010; **62**(5): 812-818.
47. Langley RG, Feldman SR, Han C, Schenkel B, Szapary P, Hsu MC *et al.* Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: Results from a

- randomized, double-blind, placebo-controlled phase III trial. *Journal of the American Academy of Dermatology* 2010; **63**(3): 457-465.
48. Bae SC, Gun SC, Mok CC, Khandker R, Nab HW, Koenig AS *et al.* Improved health outcomes with etanercept versus usual DMARD therapy in an Asian population with established rheumatoid arthritis. *BMC musculoskeletal disorders* 2013; **14**: 13.
49. Machado DA, Guzman RM, Xavier RM, Simon JA, Mele L, Pedersen R *et al.* Open-label observation of addition of etanercept versus a conventional disease-modifying antirheumatic drug in subjects with active rheumatoid arthritis despite methotrexate therapy in the Latin American region. *Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases* 2014; **20**(1): 25-33.
50. Kekow J, Moots RJ, Emery P, Durez P, Koenig A, Singh A *et al.* Patient-reported outcomes improve with etanercept plus methotrexate in active early rheumatoid arthritis and the improvement is strongly associated with remission: the COMET trial. *Annals of the rheumatic diseases* 2010; **69**(1): 222-225.
51. Guh D, Papp K, Lynde C, Bansback N, Zhang W, Qian H *et al.* Impact of adalimumab on quality of life and depression in psoriasis patients: Results from PRIDE. . *Value Health* 2010; **132010**: A148.
52. Bhutani T, Patel T, Koo B, Nguyen T, Hong J, Koo J. A prospective, interventional assessment of psoriasis quality of life using a nonskin-specific validated instrument

that allows comparison with other major medical conditions. *Journal of the American Academy of Dermatology* 2013; **69**(2): e79-88.

53. Ertenli I, Ozer S, Kiraz S, Apras SB, Akdogan A, Karadag O *et al.* Infliximab, a TNF-alpha antagonist treatment in patients with ankylosing spondylitis: the impact on depression, anxiety and quality of life level. *Rheumatology international* 2012; **32**(2): 323-330.
54. Traki L, Rostom S, Tahiri L, Bahiri R, Harzy T, Abouqal R *et al.* Responsiveness of the EuroQol EQ-5D and Hospital Anxiety and Depression Scale (HADS) in rheumatoid arthritis patients receiving tocilizumab. *Clin Rheumatol* 2014; **33**(8): 1055-1060.
55. Gossec L, Steinberg G, Rouanet S, Combe B. Fatigue in rheumatoid arthritis: quantitative findings on the efficacy of tocilizumab and on factors associated with fatigue. The French multicentre prospective PEPS Study. *Clinical and experimental rheumatology* 2015; **33**(5): 664-670.
56. Gelfand JM, Kimball AB, Mostow EN, Chiou CF, Patel V, Xia HA *et al.* Patient-reported outcomes and health-care resource utilization in patients with psoriasis treated with etanercept: continuous versus interrupted treatment. *Value Health* 2008; **11**(3): 400-407.
57. Eisenberg E, Sandler I, Treister R, Suzan E, Haddad M. Anti tumor necrosis factor - alpha adalimumab for complex regional pain syndrome type 1 (CRPS-I): a case

- series. *Pain practice : the official journal of World Institute of Pain* 2013; **13**(8): 649-656.
58. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Performance of the trim and fill method in the presence of publication bias and between-study heterogeneity. *Stat Med* 2007; **26**(25): 4544-4562.
59. Abbott R, Whear R, Nikolaou V, Bethel A, Coon JT, Stein K *et al.* Tumour necrosis factor-alpha inhibitor therapy in chronic physical illness: A systematic review and meta-analysis of the effect on depression and anxiety. *Journal of psychosomatic research* 2015; **79**(3): 175-184.
60. Capuron L, Fornwalt FB, Knight BT, Harvey PD, Ninan PT, Miller AH. Does cytokine-induced depression differ from idiopathic major depression in medically healthy individuals? *Journal of affective disorders* 2009; **119**(1-3): 181-185.
61. Capuron L, Gumnick JF, Musselman DL, Lawson DH, Reemsnyder A, Nemeroff CB *et al.* Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 2002; **26**(5): 643-652.
62. Nemeroff CB. Prevalence and management of treatment-resistant depression. *The Journal of clinical psychiatry* 2007; **68 Suppl 8**: 17-25.

63. Wium-Andersen MK, Orsted DD, Nielsen SF, Nordestgaard BG. Elevated C-reactive protein levels, psychological distress, and depression in 73, 131 individuals. *JAMA psychiatry* 2013; **70**(2): 176-184.
64. Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine* 1997; **9**(11): 853-858.
65. O'Brien SM, Scully P, Fitzgerald P, Scott LV, Dinan TG. Plasma cytokine profiles in depressed patients who fail to respond to selective serotonin reuptake inhibitor therapy. *Journal of psychiatric research* 2007; **41**(3-4): 326-331.
66. Christmas DM, Potokar J, Davies SJ. A biological pathway linking inflammation and depression: activation of indoleamine 2,3-dioxygenase. *Neuropsychiatric disease and treatment* 2011; **7**: 431-439.
67. O'Connor JC, Andre C, Wang Y, Lawson MA, Szegedi SS, Lestage J *et al.* Interferon-gamma and tumor necrosis factor-alpha mediate the upregulation of indoleamine 2,3-dioxygenase and the induction of depressive-like behavior in mice in response to bacillus Calmette-Guerin. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 2009; **29**(13): 4200-4209.
68. Litzenburger UM, Opitz CA, Sahm F, Rauschenbach KJ, Trump S, Winter M *et al.* Constitutive IDO expression in human cancer is sustained by an autocrine signaling loop involving IL-6, STAT3 and the AHR. *Oncotarget* 2014; **5**(4): 1038-1051.

69. Hodes GE, Pfau ML, Leboeuf M, Golden SA, Christoffel DJ, Bregman D *et al.* Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. *Proceedings of the National Academy of Sciences of the United States of America* 2014; **111**(45): 16136-16141.
70. Fairweather D, Frisancho-Kiss S, Rose NR. Sex differences in autoimmune disease from a pathological perspective. *The American journal of pathology* 2008; **173**(3): 600-609.
71. Kristensen LE, Kapetanovic MC, Gulfe A, Soderlin M, Saxne T, Geborek P. Predictors of response to anti-TNF therapy according to ACR and EULAR criteria in patients with established RA: results from the South Swedish Arthritis Treatment Group Register. *Rheumatology* 2008; **47**(4): 495-499.
72. Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. The safety and side effects of monoclonal antibodies. *Nature reviews Drug discovery* 2010; **9**(4): 325-338.

Figure Legends

Figure 1: PRISMA Flow Diagram of Study Selection for Systematic Review

Figure 2: Meta-analysis of Antidepressant Activity of Anti-Cytokine Treatment

Figure 3: Antidepressant Activity of Anti-TNF Treatment: Meta-analysis of RCTs

Figure 4: Meta-regression of the Association between Antidepressant Effects and Improvements in Physical Illness

Footnote: *P*-value for meta-regression slope indicates no statistically significant association between antidepressant effect of anti-cytokine treatment and improvement in physical illness. The Figure shows that the antidepressant effect does not change significantly (i.e. increase or decrease) across the range of effect estimates for physical illness.

Online Supplementary Figure 1: Meta-analysis of RCTs Using Change in Depression Score from Baseline to End of Trial

Online Supplementary Figure 2: Meta-analysis of non-randomised and/or non-placebo studies of anti-TNF treatment

Online Supplementary Figure 3: Meta-analysis of RCTs after excluding two studies (Tyring 2006 and Tyring 2013) from which data were extracted using software

Online Supplementary Figure 4: Meta-analysis of RCTs after excluding Raison et al.

Online Supplementary Figure 5: Meta-analysis of RCTs after excluding Loftus et al.

Online Supplementary Figure 6: Funnel Plot of RCTs of Anti-cytokine Drug vs. Placebo

Online Supplementary Figure 7: Funnel Plot of Non-randomized and/or Non-placebo Studies

Table 1: Clinical Trials Included in the Systematic Review of Antidepressant Activity of Anti-Cytokine Treatment

Study	Design	Drug (n)	Placebo/ comparison group (n)	Main Outcome	Drug Target	Dosage	Study Duration	Assessment of Depressive Symptoms†	Change in mean depression score from baseline‡		CONSORT Score (%)
									Treatment group	Placebo/ comparison group	
RCTs of anti-cytokine drug vs. placebo											
Tyring et al. (2006) ²⁷	Double-blind RCT	Etanercept (305)	Placebo (292)	Psoriasis	TNF- α	50mg twice weekly	12 weeks	BDI	-3.9	-2.1	94%
Loftus et al. (2008) ³⁵ [weeks 4-56]	Double-blind RCT	Adalimumab (324)	Placebo (168)	Crohn's Disease	TNF- α	40mg weekly or every other week	52 weeks	ZDS	-1.1	+1.8	53%
Langley et al. (2010) ⁴⁷	Double-blind RCT	Ustekinumab (800)	Placebo (398)	Psoriasis	IL-12, 23	45/90mg at weeks 0,4; then every 12 weeks	12 weeks	HADS-D	-1.9	+0.2	52%
Menter et al. (2010) ⁴⁶	Double-blind RCT	Adalimumab (44)	Placebo (52)	Psoriasis	TNF- α	40mg every other week	12 weeks	ZDS	-6.7	-1.6	56%

Tyring et al. (2013) ²⁶	Double-blind RCT	Etanercept (59)	Placebo (62)	Psoriasis	TNF- α	50mg twice weekly	12 weeks	PROMIS depression score	-5.5	-2.7	*
Raison et al. (2013) ²⁰	Double-blind RCT	Infliximab (27)	Placebo (28)	Treatment-resistant depression	TNF- α	5mg/kg at weeks 0,2 and 6	12 weeks	HAM-D	-7.5	-9.6	91%
Simpson et al. (2015) ⁴⁵	Double-blind RCT	Dupilumab (318)	Placebo (61)	Atopic Dermatitis	IL-4R- α	Variable (100 to 600mgs every one to four weeks)	16 weeks	HADS	-4.2	+0.1	*
RCTs of anti-cytokine drugs as adjuncts to an active treatment											
Kekow et al. (2010) ⁵⁰	Double-blind RCT	Etanercept + DMARD (265)	DMARD (263)	Rheumatoid arthritis	TNF- α	50mg weekly	52 weeks	HADS-D	-2.4	-2.0	48%
Bae et al. (2013) ⁴⁸	Randomised open-label	Etanercept + DMARD (192)	DMARD (100)	Rheumatoid arthritis	TNF- α	25mg twice weekly	16 weeks	HADS-D	-2.2	-1.3	63%
Machado et al. (2014) ⁴⁹	Randomised open-label	Etanercept + DMARD (279)	DMARD (142)	Rheumatoid arthritis	TNF- α	50 weekly	24 weeks	HADS-D	-2.8	-1.9	77%
Non-randomised and/or non-placebo trials											
Minderhoud	Single-	Infliximab	-	Crohn's	TNF- α	5mg/kg at	4 weeks	CES-D	-5.7	-	-

et al. (2007) ³⁸	blind	(14)		Disease		baseline					
Loftus et al. (2008) ³⁵ [weeks 0-4]	Open-label	Adalimumab (499)	-	Crohn's Disease	TNF- α	80mg at baseline; 40mg at week 2	4 weeks	ZDS	-9.1	-	-
Gelfand et al. (2008) ⁵⁶	Open-label	Etanercept (2546)	-	Psoriasis	TNF- α	50mg twice weekly	12 weeks	BDI	Not reported	-	-
Dauden et al. (2009) ³⁷	Randomi sed (to dosage regimen), open- label	Etanercept (703)	-	Psoriasis	TNF- α	25 or 50mg twice weekly	54 weeks	HADS-D	-1.6	-	-
Guh et al. (2010) ⁵¹	Open-label	Adalimumab (174)	-	Psoriasis	TNF- α	80mg at baseline; 40mg every other week	24 weeks	BDI	-4.4	-	-
Ertenli et al. (2012) ⁵³	Open-label	Infliximab (16)	-	Ankylosin g spondylitis	TNF- α	5mg/kg at weeks 0, 2 and 6	6 weeks	HADS-D	-3.0	-	-
Gniadecki et al.	Randomi sed (to	Etanercept (752)	-	Psoriasis and	TNF- α	50mg weekly;	12 weeks	HADS-D	-1.5	-	-

(2012) ³⁶	dosage regimen) double-blind			psoriatic arthritis		50mg twice weekly					
Bhutani et al. (2013) ⁵²	Open-label	Adalimumab (32)	-	Psoriasis	TNF- α	80 to 40mg every other week	24 weeks	PGWB depression	-1.9	-	-
Eisenberg et al. (2013) ⁵⁷	Open-label	Eisenberg (9)	-	Complex regional pain syndrome type 1	TNF- α	40mg twice every other week	4 weeks	BDI	Not reported	-	-
Traki et al. (2013) ⁵⁴	Open-label	Tocilizumab (26)	-	Rheumatoid arthritis	IL-6R	8mg/kg monthly	26 weeks	HADS-D	-1.0	-	-
Gossec et al. (2015) ⁵⁵	Open-label	Tocilizumab (610)	-	Rheumatoid arthritis	IL-6R	-	-	HADS-D	-1.3	-	-

Note: † BDI = Beck's Depression Inventory, CES-D = Center for Epidemiological Studies Depression Scale, HAM-D = Hamilton Depression Rating Scale, HADS(-D) = Hospital Anxiety and Depression Scale (Depression), PGWB depression = Psychological General Well-Being depression, ZDS = Zung Depression Inventory; * could not assess fully because articles published as a letter or as a conference abstract (data from Tying *et al* was extracted using software and from Simpson *et al* by contacting authors directly); ‡ (-)ve = decrease in depression score from baseline, (+)ve = increase in depression score from baseline