Tumour necrosis factor α inhibitor therapy in chronic physical illness: a systematic review and meta-analysis of the effect on depression and anxiety.

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Abstract

Objective

Depression is more common among individuals with chronic physical illness than in the general population. New treatments for severe and chronic inflammatory conditions which inhibit tumour necrosis factor alpha (TNFα), a pro-inflammatory cytokine, may be able to shed some light on the role of inflammatory mediators in depression. This systematic review and meta-analysis of randomised controlled trials determined the effects of TNFα inhibitor therapy on depression and anxiety in people with chronic physical illness.

Methods

Seven databases were searched from inception to January 2014: AMED, Central, Cochrane Database of Systematic Reviews, CINAHL, Embase, MEDLINE, and PsycINFO. Articles were screened for inclusion independently by two reviewers. Data extraction and appraisal were conducted by one reviewer and checked by a second. Random-effects meta-analyses were performed.

Results

Six randomised controlled trials (reported in seven articles) met eligibility criteria and were included in the final review. In total 2540 participants were enrolled across the trials, with participants presenting with rheumatoid arthritis (n=3 trials), psoriasis (n=2) or ankylosing spondylitis (n=1). Meta-analyses, using standardised mean differences, showed evidence of small reductions in depression (-0.24; 95% CI -0.33 to -0.14; p <0.001), and anxiety (-0.17; 95% CI -0.31 to -0.02; p=0.02).

Conclusion

TNFα inhibitor therapy reduces depression in people with chronic disease though the effects are small. Whilst this is consistent with inflammation contributing to the development of

depression, further studies investigating a more detailed timeline of changes in depression,

inflammatory biomarkers and disease activity status are required.

1.0 Introduction

Depression is two to three times more common in people with chronic physical illnesses than in the general population [1]. This is of particular concern as depression is associated with a range of adverse outcomes among people with chronic physical illnesses, including increased mortality [2-4], increased morbidity [5, 6], poorer health-related quality of life [7-9], and increased healthcare use and costs [10, 11]. The causes of depression in the physically ill are complex and multifactorial. General risk factors, such as being female, having a family or personal history of depression, having markers of social deprivation, a lack of social support and marked psychosocial stresses are known to be predictive of depression [12]. Factors relating to the illness and its treatment also influence who develops depression, such as negative beliefs about illness [13], the presence of pain [12, 14], disability [15, 16] and unpleasant side-effects from treatment [17]. Understanding the causes of depression is of central importance in the management of individuals with chronic physical illnesses as it offers the opportunity to: i) identify those at greatest risk of additional illness burden due to depression, ii) identify those at risk of worse medical outcomes and iii) potentially reduce the risks of adverse medical outcomes, either by treating depression or increasing the intensity of medical management.

Recently there has been growing interest in the roles of inflammation in contributing to the development of depression in people with physical illness [18, 19]. Depression is associated with an increase in biomarkers of inflammation, including c-reactive protein (CRP), interleukin 1 (IL-1), interleukin 6 (IL-6) and tumour necrosis factor alpha (TNFα), in clinical and community populations [20] ADD HIMMERICK REF. Epidemiological studies have demonstrated that depression is predicted by higher levels of inflammatory mediators [21],

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though such prospective associations have not been consistently observed with some finding depression predicting inflammation [22]. Controlled, experimental studies in healthy volunteers, in which inflammation is triggered by the acute administration of an endotoxin or attenuated vaccine, have demonstrated transient increases in the symptoms of depression associated with increases in IL-1 receptor antagonist (IL-1Ra), IL-6 and tumour necrosis factor alpha (TNFα) [23, 24]. Furthermore, administration of Interferon alpha, which greatly increases the level of inflammatory mediators, is associated with development of major depression in up to one third of patients [25], which is preventable in many by pre-treatment with antidepressants [26, 27]. Whilst such observational studies and short-lived experimental studies provide evidence that inflammatory mechanisms contribute to the development of clinically significant depression in people with chronic physical illness, they fall short of proving the causal link.

The recent development of pharmacological agents which specifically inhibit the inflammatory mediator TNFα, a pro-inflammatory cytokine, offer a new means of investigating the links between inflammation and depression [28]. Administration of TNFα inhibitors have resulted in a reduction of depression-like and anxiety-like symptoms in rodent models of depression (Camara 2015, Krugel 2013). In clinical studies, TNFα inhibitors have been shown to improve outcomes in a high proportion of people with severe inflammatory disorders, who have failed to respond to other treatments. Indeed, TNFα inhibitors have also been shown to improve depressive symptoms among people with chronic inflammatory disorders [29], though this does not always appear to be the case [30]. More recently, Arisoy and colleagues [31] have shown that patients with ankylosing spondylitis who were treated with TNFα inhibitors reported a significant decrease in

depression which, importantly, was not associated with changes in markers of clinical disease activity. They, and others [32], have suggested that the improvements in depression but not markers of clinical disease activity, provides support for an inflammatory mechanism underpinning the development and maintenance of depression. Although the link between anxiety and inflammation has been much less studied, with recent findings of correlations between inflammatory markers and anxiety disorders and increased inflammatory activation in patients with anxiety disorders [33], anxiety was included as a secondary outcome of interest.

The purpose of this systematic review therefore, was to determine whether TNFα inhibitor therapy in people with chronic physical illness reduces symptoms of depression and anxiety. Further, the review sought to explore the relationship between timing of change in depression and anxiety symptoms with change in either immunological or clinical status.

2.0 Methods

The systematic review was conducted following the general principles published by the NHS Centre for Reviews and Dissemination [34] and has been reported in accordance with the PRISMA statement [35]. The protocol was registered with Prospero in September 2013 (registration no. CRD 42013006068).

2.1 Types of studies

Only randomised controlled trials (RCTs) were considered eligible for the purposes of this review.

2.2 Types of participants

Individuals with a chronic physical illness undergoing treatment with a TNF-α inhibitor (this was likely to include, but was not exclusive to, conditions such as rheumatoid arthritis, psoriasis, crohn's disease and ankylosing spondylitis). Studies which involved participants being treated for mental illness alone were not eligible.

2.3 Types of interventions

The intervention of interest was treatment with TNFα inhibitors, compared against usual care (treatment with a non TNFα inhibitor) or control. At the time of the review, the available TNFα inhibitors were Etanercept, Infliximab, Adalimumab, Certolizumab, and Golimumab. Studies that simply compared two doses of TNFα inhibitors (with no control or usual care arm), or studies that assessed attenuation/escalation of TNFα inhibitors doses, in which both intervention arms received at least one dose of TNFα inhibitors were not considered eligible for inclusion.

2.4 Outcome measures

The primary outcome of interest in this review was depression, assessed using a validated psychological measure, such as the Hospital Anxiety Depression Scale (HADS), and the Beck Depression Inventory (BDI). A list of recognised measures of depression was agreed *a priori* (CD and RA). Self-reported measures of mental health related quality of life were not considered eligible. Secondary outcome measures of interest were anxiety, assessed with a recognised psychological measure, and measures of inflammatory and clinical disease status (only in relation to the timing of any changes in depression observed).

2.5 Search Strategy

The search strategy was developed by an information specialist (AB) in consultation with topic and methods experts (CD, BA, BW, JTC). The strategy used a combination of MeSH terms and free text terms, including terms for TNFα inhibitor or agonist, including the named drugs, and terms describing depression. An illustration of the exact search strategy used on MEDLINE can be seen in Figure 1. Seven databases were searched from inception to January 2014: AMED, Central, Cochrane Database of Systematic Reviews, CINAHL, Embase, MEDLINE, and PsycINFO. No date or language restrictions were used. We also searched ClinicalTrials.gov for recently completed and ongoing studies. Forward and backward citation chasing of each included article was conducted. Two reviewers (RA, with RW or AB) independently screened titles, abstracts and full texts using the eligibility criteria. Discrepancies were discussed and resolved by a third reviewer (RW or AB) where necessary.

2.6 Risk of bias and study quality

The methodological quality of each paper was assessed using the Cochrane 'risk of bias' tool [36]. The tool includes six key criteria against which potential risk of bias is judged: adequacy

of allocation sequence generation; adequacy of allocation concealment; blinding of participants, personnel or outcome assessors; completeness of outcome data; selectivity of outcome reporting, and other bias. In addition to the Cochrane risk of bias tool, four additional aspects of quality relating to reporting of eligibility criteria, similarity of baseline characteristics, compliance with intervention and data collection tool validity were assessed. Quality was assessed by one reviewer (RA, AB, or RW), with judgements checked by a second (RW, RA, or AB). Any discrepancies were discussed and resolved.

2.7 Data collection

Data on the study design, the setting, the population, the intervention, the outcomes and results, and risk of bias were collected using a standardised, piloted data extraction form. Data were extracted by one of two reviewers (RA, AB) and fully checked by another (RA or RW).

2.8 Data analysis and synthesis

Random effects meta-analyses were performed where we had sufficient data from RCTs for the effect of intervention on the outcome measures of depression and anxiety. Pooling was performed on the post intervention outcome measurement. As we used a random-effects model for the meta-analyses, the weightings for each study were determined not only by the size of each study included, but also by the estimate of between-study heterogeneity. All studies assessing depression, analysed change in outcome between baseline and post intervention. Across the six trials there were four different scales used to assess depression, and one study [37] only reported an adjusted standardised effect size between interventions and control, Therefore, in all but one study [37], unadjusted post-intervention summary data were used to calculate standardised effect sizes (ES) between groups. In the

case of the Tyring et al. study [38], where two different scales were used to measure the same outcome from the same population, we computed a single effect size as the mean of the effect sizes of the two scales and a variance that takes into account the correlation between the two scales [39]. As some have queried the interpretability of standardised effect sizes [40], we also performed a random effects meta-analysis on the non standardised mean differences data for studies in which the same depression scale only had been used. Data for this analysis is reported as the pooled mean difference with 95% confidence intervals. Anxiety was measured across the studies using the same assessment tool; however, as only the adjusted standardised effect size between groups was reported in one study [37], pooled effects are reported as standardised effects sizes with 95% confidence intervals. Heterogeneity across estimates was quantified using the I-squared statistic and tested using the Q-statistic [41]. Synthesised results are presented by outcome type. Effect sizes are expressed as small (0.2-0.5), moderate (0.5-0.8) and large (>0.8) [42]. Where pooling was not appropriate or possible, the findings have been summarised in narrative form.

Data analysis was carried out using Stata [Stata Corporation. Stata Statistical Software. Release 12.1. College Station,TX, 2011] and Review Manager (RevMan) Version 5.2 software (http://ims.cochrane.org/revman). Synthesised results are presented by outcome type. Effect sizes are expressed as small (0.2-0.5), moderate (0.5-0.8) and large (>0.8) [42]. Where pooling was not appropriate or possible, the findings have been summarised in narrative form.

3.0 Results

The electronic searches found a total of 1351 results, 360 of which were duplicates, leaving 991 titles and abstracts to screen. After double screening of each one, 28 full texts were retrieved for closer examination. A total of seven articles (from six trials) were included in the final review, with two identified from forward and backward citation chasing. Reasons for exclusion at the full text stage can be seen in Figure 2. The ASCEND trial was reported in two articles: a UK group subset only [43], and the full multicentre study [37]. Data from the full study were used for all analyses where possible.

3.1   Study characteristics

All included articles reported on multi-centre randomised controlled trials conducted across more than one country. Trial size ranged from 48 to 620 participants, with five of the six trials having >300 participants [30, 37, 38, 44, 45]. In total, 2540 participants were enrolled across the six trials. Participants were those presenting with rheumatoid arthritis (n=3 trials) [30, 44, 45], psoriasis (n=2) [38, 46], and ankylosing spondylitis (n=1) [37, 43]. The mean age of participants recruited ranged from 41 to 51 years, and all trials were of mixed sex. All six trials were primarily safety and efficacy studies (the main clinical and safety findings being presented elsewhere) in participants with moderate to severe chronic disease, with depression being assessed as a secondary outcome measure. Only one study [38] reported excluding participants with psychiatric disease, and the same study also reported the intention to withdraw any patients who became actively suicidal during the trial. Three studies [30, 38, 46] reported prevalence of depression and anxiety at baseline, and the mood state in these populations were found to be representative of other studies of populations with chronic disease, ranging between 16-47% of participants showing some

degree of clinical depression and/or anxiety. None of the studies proactively recruited participants with depression.

3.2   Intervention characteristics

All six trials excluded anyone that had previously received TNFα inhibitor treatment. The three trials for participants with rheumatoid arthritis all assessed the TNFα inhibitor etanercept. Etanercept was used in conjunction with methotrexate and compared against the standard disease modifying anti-rheumatic drug (DMARD) of choice plus methotrexate in two open-label RCTS [44, 45], and against methotrexate alone in the third double-blind RCT [30]. Trial length ranged from 16 to 52 weeks. The two trials for participants with psoriasis were both placebo controlled double-blind trials and assessed the effects of adalimumab [46] and etanercept [38] respectively. Both trials were of 12 weeks duration. The trial for those with ankylosing spondyitis was a 4 month long double blind study, reported in two articles, comparing etanercept to sulphasalazine [37, 43]. All six trials found significant clinical benefit of TNFα inhibitor treatment compared to comparator treatment [30, 38, 44, 45, 47, 48].

3.3   Psychological outcome measure

Depression was assessed as a secondary outcome in all six trials. Four of the trials used the Hospital Anxiety and Depression Scale (HADS) [30, 37, 43-45], one used the Zung Depression Scale (ZDS) [46] and one trial used two different scales: the Hamilton Rating Scale for Depression (HAM-D) and the Beck Depression Inventory (BDI) [38]. Anxiety was also assessed as a secondary outcome in four trials, with HADS as the assessment tool [30, 37, 43-45].

3.4   Study Quality (risk of bias)

A summary of the risk of bias is presented in Figure 3. For a few trials, some of the information for this, where referred to and available, was taken from the 'parent' primary outcome paper [47-50] which described the trial methodology in more detail. Whilst all six included articles were RCTS, the studies were not without issues relating to possible bias. For the majority of studies, the methods of randomisation and selection of eligibility criteria were well described. Four of the trials were double blind and for these studies, there was little risk of bias with regards to blinding of participants and outcome assessments. However, two open-label studies were susceptible to bias of outcome measurement, but these limitations were recognised in both papers. For most of the studies, outcome data were complete or missing data were accounted for adequately, however none of the studies reported on compliance with the intervention. Data collection tools for depression and anxiety were all valid and reliable. All articles were presenting data that was secondary to the primary aim of the trial, and all articles included authors that were either employed by a pharmaceutical company or had received monies from pharmaceutical industry, though the degree to which they were involved in data interpretation and analysis was not stated for any of the articles.

3.5   Effects on depression

Data from all six trials were included in the meta-analysis on the effects of treatment on depression. TNFα inhibitor therapy was found to have a significant beneficial effect on depression across a variety of clinical populations in five of the six trials, showing small to medium effects. Pooling the studies together, irrespective of the depression assessment tool used, we found a small but statistically significant effect size of -0.24 in favour of the intervention group (95%CI: -0.33 to -0.14; p<0.001). The heterogeneity between studies (38%) was not statistically significant (p = 0.15). The forest plot for this analysis is shown in

Figure 4. Repeating the analysis to include only studies that reported non standardised data utilising the same depression assessment tool, resulted in comparable findings: the pooled effect of TNFα inhibitor treatment on depression in people with rheumatoid arthritis, as measured by HADS [30, 44, 45], resulted in an overall mean difference in HADS of -0.65 (95%CI: -1.15 to -0.16, p=0.009) in favour of the intervention group; this equates to a pooled standardised mean difference of 0.16, in the three studies included in this sub-analysis. There was 12% heterogeneity between the three studies which was not statistically significant (p = 0.32).

Two studies [38, 46] assessed whether there was an association between change in depression and change in clinical disease status. Menter et al. [46] found a significant correlation between the two, whilst Tyring et al. [38] found no strong correlation in the two outcomes. Neither of the studies however assessed depression frequently enough to determine whether the changes in depression appeared prior to changes in clinical disease status. None of the studies reported analysing depression in relation to inflammatory markers.

3.6   Effects on anxiety

Four studies provided data suitable for meta-analysis. Three studies were in populations with rheumatoid arthritis, and one in a population with ankylosing spondylitis and all used HADS as the assessment tool. The pooled effect of TNFα inhibitor treatment on anxiety resulted in an overall standardised mean difference of -0.17 in favour of the intervention group which was statistically significant at 5% level of significance, 95%CI: -0.31 to -0.02; p = 0.02 (forest plot shown in Figure 5). There was 61.7% heterogeneity between the four studies which was borderline statistically significant (p = 0.05).

4.0 Discussion

This is the first systematic review and meta-analysis of the effects of TNFα inhibitor treatment on depression and anxiety in people with chronic inflammatory disease. Data from six randomised trials (reported in seven articles), involving a total of 2540 participants with moderate to severe chronic inflammatory disease, showed a small but statistically significant effect of TNFα inhibitor treatment on reducing depression. Although not measured in all studies, a significant beneficial effect of intervention was also observed for anxiety. The association between improvement of depression with improvement in inflammatory condition was inconsistent, however; one study reported an association between clinical improvement and improvement in depression, whereas another study observed no association between the two. None of the studies were able to determine whether the changes in depression occurred independent of, or prior to, any changes in markers of clinical disease activity.

The review followed best practice guidelines for systematic reviews [34] and did not restrict by date or language, nor by whether studies had been published or not. Authors of papers who had published abstracts only, were contacted for their data, if available. Only data from placebo (or usual care) controlled RCTs were eligible for this review, to enable us to draw inferences about the causal relationship between use of TNFα inhibitors and improvements in depression. We pooled study findings using standardised mean differences, to enable us to combine findings using differing measures of depression and anxiety, but also presented findings for the majority of studies using the same measure using weighted mean difference, to aid interpretation. Importantly, the effect size of TNFα inhibitor treatment on depression was comparable irrespective of the meta-analytic approach taken.

With regards to potential weaknesses, this review included RCTs for which the primary aim had to been to assess safety and efficacy of treatment on physical health status. Whilst the designs of the included studies were robust, the primary aims of the trials were not to establish effects on psychological status, nor to relate this to clinical disease status and inflammatory biomarkers. Whilst this may be interpreted as meaning that less effort and rigour may have been invested in the assessments of depression, all the measures used were well-validated. Importantly, the self-rated assessments performed similarly to the observer rated HAM-D measure of depression in the one trial that used both forms of assessment [38], which suggests that reliance on self-rated depression measures in the majority of studies did not inflate the observed effects of TNFα inhibitors on depression. Also by focusing on secondary outcomes of trials, it could be argued that our findings are less likely to be influenced by publication or reporting bias. Another possible limitation for this review is the small number of studies that the review located. Although the trials were of reasonable size, and data from more than 2500 participants, was pooled for example for analysis of the effects of TNFα on depression, this does only represent six studies, and therefore the results need to be interpreted with caution. A further consideration must be given to the fact that whilst the populations included in the studies were similar on the grounds that they were receiving TNFα inhibitor therapy for an inflammatory condition, there is likely to have been considerable variation in the disease states, and the factors impacting on depression and anxiety of the participants within each trial, and across the trials of different chronic diseases. Some small reassurance is given by the three studies that reported baseline mood state, which were found to be representative of other studies of populations with chronic disease.

We interpret our findings as indicating that treatment with TNFα inhibitors in people with chronic inflammatory conditions improves depression and anxiety. The effects of TNFα inhibitors on depression were small, however, and whilst there is no established minimum clinically important difference for the HADS depression scale, the small effect observed would be below what most would consider to be clinically significant. Such a small effect could indicate that other, non- TNFα mediated mechanisms were important determinants of depression among the patients studied. However, a number of methodological characteristics of the included studies could also have influenced the size of observed effect. First, these small effects could be attributable, at least in-part, to the fact that the included studies did not specifically recruit patients with depression or anxiety (one study even excluded people with significant psychopathology). The prevalence of depression and anxiety (in the three studies where these were reported) were between 16-47%, meaning that the majority of patients were not depressed, thereby limiting the potential for antidepressant effects. Secondly, in the control arm of most of the included trials, active anti-inflammatory drugs (treatment as usual) were used which may have reduced the apparent effects of TNFα inhibitors. Effects in trials using placebo control were not systematically greater than those that had used active treatment however, suggesting this is unlikely to have influenced the findings of this review.

Other randomised studies of TNFα inhibitor treatment in chronic disease have reported effects on depression of greater magnitudes to that found in this review. Studies which have randomised patients with psoriasis to either paused or continuous etanercept treatment, or varying doses of etanercept, found 25-30% improvement in HADS depression scores, between a 1.5 -2.0 decrease (compared to our mean effect difference in our review of 0.65) [51, 52]. Whist the intervention groups in the RCTs in our present review also saw

decreases in depression of similar magnitude (i.e. of between 1.0-3.0 in HADS depression score), depression scores in the control groups in our included studies were also found to improve, albeit by less, hence the lower overall mean effect difference. Loftus, in their study randomising individuals to different doses of adalimumab for Crohn's disease, found a significant reduction in depression (9 points on the ZDS), slightly higher than that reported in the study by Menter et al., included within this review [53]. Of interest, the regimes used in these dosing studies were comparable and/or higher to those used in the studies in this present review, however none of them observed greater responses with the higher doses. Whilst these trials comparing different doses of the TNFα inhibitors were excluded by our *a priori* criteria, their findings are in agreement with a small but significant effect of TNFα inhibitors on depression.

Whilst our review provides evidences that treatment with TNFα inhibitors improves depression, it fails to indicate whether the mechanisms of improving depression are directly mediated by a reduction in TNFα or whether the benefits to depression are secondary to reductions in pain and disability associated with improvement in chronic inflammatory condition. None of the included studies provided sufficient detail of the timing of changes in depression relative to the changes in clinical disease status to determine whether improvements in mood predate improvements in markers of clinical status. In the study by Tyring et al. [38], there was a lack of a strong correlation between the improvements in depression and in markers of clinical disease status, which led the authors to conclude that treatment affected depression directly (i.e. not secondary to improvements in clinical status).

Raison et al. [54] have recently considered the mechanism of effect of TNFα inhibitors on depression in the first published RCT of TNFα inhibitor therapy (infliximab) for individuals

with treatment resistant depression. They found that Infliximab had no overall effect on depression in the sample as a whole. Whilst individuals with diagnosed autoimmune disorders were excluded, the authors did find reductions in depression among subjects with higher baseline levels of inflammation (hs-CRP>5mg/L). In addition to this, a case study of TNFα inhibitor therapy (infliximab) for five individuals with late onset depressive disorder, found no effect on depression in four individuals, but complete disappearance of depressive symptoms in the only patient with a comorbid inflammatory condition [55]. The findings of both of these studies are consistent with the conclusion that TNFα inhibitors improve depression directly via inflammatory pathways, though both fall short of proving this mechanism of effect.

Future research needs to take the extant findings and start to tease out the some of the unknown issues highlighted. For example, would anti-inflammatory treatment benefit certain subgroups of populations with depression who present with elevated inflammatory biomarkers. As such, might existing levels of TNFa in individuals with depression indicate who is likely to respond to anti-inflammatory therapy, or might some other inflammatory biomarker be more appropriate. In terms of trying to tease out cause and effect, is it possible with more detailed investigations into the timeline of changes to both clinical indicators of disease and biomarkers of inflammatory status to see how inflammation impacts depression and anxiety.

Conclusion

In summary, TNFα inhibitor therapy reduces depression and anxiety in people with chronic disease. Whilst this is consistent with a proposed inflammatory mechanism of depression, further studies are require to establish the mechanism of effect, by investigating a more

detailed timeline of changes in depression, clinical markers of disease activity status and inflammatory biomarkers, and the extent to which improvements in depression correlate with improvements in clinical and inflammatory status.

Competing interests

The authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

Contribution of authors

CD conceived the concept of the study and all authors contributed to the protocol of the study. RA, RW and AB screened and data extracted the literature. VN performed the data analyses, RA drafted the manuscript, and all authors commented on subsequent drafts and contributed to the interpretation, discussion and implications.

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Table 1. Study characteristics and summary of main depression and anxiety outcome data

Author	Location	Population (including prevalence of depression & anxiety)	Intervention	Depression & anxiety measure	Findings (Intervention vs Comparator)
Bae 2013 **APPEAL study**	Multi (Hong Kong, India, Malaysia, Philippines, Taiwan, Korea and Thailand)	300 adults with rheumatoid arthritis (who showed inadequate response to oral MTX), mean age 48yrs Baseline depression prevalence not reported	Open-label study. ETN (25mg 2/week) + MTX (n=197) vs DMARD + MTX (N=103) for 16 weeks	HADS	Depression improvement: 7.62 to 5.42 (-28.7%) for ETN vs 7.85 to 6.56 (-16.4%) for DMARD, p=0.016 Anxiety improvement: 29.1%(ETN) vs 18.5% (DMARD) improvement, p=0.026
Kekow 2010 **COMET study**	Multi (Europe, Latin America, Asia, Australia)	528 adults with early active rheumatoid arthritis, mean age 51yrs Baseline depression: 47% Baseline anxiety: 37%	Double blind study. ETN (50mg 1/week) + MTX (n= 265) vs MTX (n=263) for 52 weeks	HADS	Depression no significant change: 6.82 to 4.39 (-2.43) for ETN vs 6.68 to 4.66 (-2.02) for MTX, Not Significant (NS) Anxiety no change: -2.12(ETN) vs -1.92 (MTX) improvement, NS
Machado 2014	Multi (Argentina, Chile, Columbia, Mexico, Panama)	429 adults with rheumatoid arthritis (who showed inadequate response to MTX), mean age 48yrs Baseline depression prevalence not reported	Open label study. ETN (50mg 1/week) + MTX (n=284) vs DMARD + MTX (n=145) for 24 weeks	HADS	Depression improvement: adjusted mean change: -2.8 (0.2) for ETN vs -1.9 (0.3) for DMARD, p=0.0077 Anxiety no change: -2.2(0.3) for ETN vs -1.7 (0.3) for DMARD, p=0.16
Menter 2010	Multi (USA and Canada)	97 adults with psoriasis, mean age 44yrs Baseline depression: 35%	Double blind study. ADM (40mg 1/week) (n=45) vs Placebo (n=52) for 12 weeks	ZDS	Depression improvement: 42.9 (12.4) to 36.2 (11.5) for ADAL vs 45.8 (14.0) to 44.2 (14.2) for placebo, Difference in change -6.0 (-9.5 to -2.5), p=0.001 (*Improvement in ZDS correlated with improvement in physical symptoms (r=0.5, p<0.001), but not able to assess which came first*)

Packham 2012 **ASCEND study ****	Multi (centres across the UK)	Subgroup of 48 adults with ankylosing spondylitis in UK, mean age 41yrs Baseline depression prevalence not reported	Double blind study. ETN (50mg 1/week) (n=29) vs SLZ (n=19) for 16 weeks	HADS	Depression improvement: effect size (ES) greater for ETN, n=29, (ES – 0.86) compared to SSZ, n=15 (ES – 0.39), *no statistics presented* Anxiety no change: ES similar between 0.68 (ETN) vs 0.81 (SSZ), *no statistics presented*
Tyring 2006	Multi (USA and Canada)	620 adults with psoriasis, mean age 46yrs Baseline depression: 19% mild, 15% moderate (BDI); 24% mild, 2% moderate (HAM-D)	Double blind study. ETN (25mg 2/week) (n=311) vs Placebo (n=309) for 12 weeks	HAM-D and BDI	Depression: i) HAM-D Depression improvement ETN vs Placebo, 1.5 vs 0.4, (CI 0.4-1.9, p=0.0012), ES of 0.25 2) BDI Depression Improvement ETN vs Placebo, 1.8, (CI 0.6-2.9, p<0.001), ES of 0.22. *(Changes in depression not strongly correlated with objective clinical measures.)*
Van der Heijde 2012 **ASCEND study ****	Multi (Europe, Latin America, Asia, Australia)	566 adults wit ankylosing spondylitis, mean age 41yrs Baseline depression prevalence not reported	Double blind study. ETN (50mg 1/week) (n= 379) vs SSZ (n= 187) for 16 weeks	HADS	Depression improvement: Greater improvement in ETN vs SSZ: -0.7 (3.0), p <0.05 Anxiety improvement: Greater improvement in ETN vs SSZ: -0.6 (3.0) , p <0.05

** same study

Drug:
ADM - Adalimumab
DMARD – Disease modifying anti rheumatic drug
ETN – Etanercept
MTX – Methotrexate
SSZ - Sulphsalazine

Assessment tools:
BDI – Beck Depression Inventory
HADS – Hospital Anxiety and Depression Scale
HAM-D Hamilton's Rating Scale for Depression
ZDS – Zung's self-rating Depression Scale

Legends for Figures

Figure 1: Example of search strategy used on Medline.

Figure 2: PRISMA flow diagram showing identification of included studies.

Figure 3: Cochrane risk of bias table of included studies.

Figure 4: Forest plot showing the results of the meta-analysis on the effects of TNFa

inhibitor treatment on depression.

Figure 5: Forest plot showing the results of the meta-analysis on the effects of TNFa

inhibitor treatment on anxiety.