

USING NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN THE TREATMENT OF DEPRESSION

Abigail Davis¹, Michael Gilhooley² & Mark Agius^{3,4}

¹Wexham Park Hospital, UK

²University of Glasgow, UK

³Department of Psychiatry, University of Cambridge, UK

⁴South Essex Partnership University Foundation NHS Trust, UK

SUMMARY

Background: Clinicians have long noticed a correlation between physiological markers of inflammation and depression. The best-known example is the activation of the hypothalamus-pituitary-adrenal axis and cortisol secretion; however more recent studies have demonstrated increased salivary prostaglandins and plasma acute phase proteins in depressed patients.

To date four randomised controlled trials have used celecoxib or rofecoxib as adjuncts to serotonin selective reuptake inhibitors in the treatment of depression. These suggested a statistically significant decrease in depressive symptoms in the patients taking NSAIDs and SSRIs, compared to patients taking SSRIs alone.

Interpretation of these results is limited by the small sample size and short duration of these preliminary studies. The research only considers depressed patients receiving treatment in secondary care; no study has examined the effectiveness of NSAIDs as an adjunct in primary care, even though most cases of depression in the UK are managed in the community by general practitioners.

Proposal: We propose a multi-centre double-blinded randomised controlled trial with two objectives: to determine whether citalopram plus celecoxib dual therapy achieves a greater reduction in depressive symptoms (quantified using the Hamilton Depression Rating Scale (HDRS)) within four weeks, compared to citalopram monotherapy; and to determine whether citalopram plus celecoxib dual therapy is more likely to achieve remission (HDRS score ≤ 7) of moderate to severe depression within six months, compared with citalopram monotherapy.

The endpoints will be the reduction in HDRS score after 4 weeks of treatment, and the HDRS score after 26 weeks of treatment.

The study will enrol 452 participants from general practices who have a moderate or severe, current or recurrent major depressive episode when medication with an SSRI is considered.

The study population will be stratified according to age, sex, HDRS score, age of onset of first episode, number of previous depressive episodes and duration of current episode. The population will then be randomised into two groups.

Subjects will be interviewed to determine HDRS score, measure blood pressure, count pills and discuss side-effects. This will occur weekly for the first four weeks, and every four weeks thereafter.

Key words: depression - non-steroidal anti-inflammatory drugs - anti-depressants - cytokines

* * * * *

Introduction

We present a brief review of the current literature regarding the use of Non-Steroidal Anti-Inflammatory drugs (NSAIDs) as adjuncts in the treatment of depression, and propose a UK-based multicentre trial to expand the evidence base for this therapy.

Background

Many physiological changes are observed in patients with depression, and our understanding of the bridge between physiology and psychiatry is ever increasing. Perhaps the best characterised link is the activation of the hypothalamic-pituitary-adrenal axis in response to stress (Nemeroff et al. 2005); however, activation of inflammatory pathways may also contribute to the symptoms of depression. Administration of a pro-inflammatory cytokine (interferon- α) as a therapeutic agent (Raison et al. 2006) can induce a syndrome which is strikingly similar to major depressive disorder and responsive to standard antidepressant therapies,

suggesting that a systemic inflammatory response may be a contributing factor to some cases of depression.

Depressed patients without medical co-morbidity have increased plasma levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) (Berk et al. 1997) and of the acute phase protein C-reactive Protein (CRP) (Berk et al. 1997). Increased salivary concentrations of prostaglandin E2 (PGE2) have also been found in depressed subjects compared to healthy controls (Ohishi et al. 1998). Inhibitors of cyclooxygenase-2 (COX-2), the enzyme which synthesises PGE2, are commonly used in clinical practice as analgesics and anti-inflammatories; studies have noticed an incidental improvement in depressive symptoms in patients treated with the COX-2 inhibitor rofecoxib for comorbid osteoarthritis (Collantes-Estevéz et al. 2003).

Existing evidence from clinical trials

Four clinical trials have evaluated the use of NSAIDs as adjuncts in pharmacotherapy for depressions.

Muller et al. (2006) studied 40 patients, all of whom were diagnosed with unipolar depression (DSM-IV). Both groups were matched for sex, age, age of onset, number of depressive episodes and duration of present episode, reboxetine dose, and benzodiazepine dose. After a three-day washout period, 20 patients received reboxetine, titrated to clinical need, and 20 received reboxetine plus celecoxib (400mg/day). There was a statistically significant decrease in depressive symptoms, measured using the Hamilton Depression Rating Scale, in both groups. Plasma reboxetine levels were not significantly different between the groups. However 22 patients dropped out of the study, citing the noradrenergic side effects of reboxetine. None of the patients experienced adverse effects from celecoxib. In the fifth week of the study there was a significant difference in Hamilton score between the groups; over the whole six week period there was a trend to significance, favouring the reboxetine and celecoxib combination.

Mendlewicz et al. (2006) studied 21 patients who had not responded to serotonin-selective reuptake inhibitors after 4 weeks monotherapy. The patients received 160mg/day of acetylsalicylic acid in addition to their current antidepressant therapy. 11 patients responded in the first week and sustained the response throughout the four weeks of the trial, showing a significant reduction in Hamilton Depression Rating Scale (HDRS) score. Of the patients who responded, 8 had unipolar depression (DSM-IV) and 3 had bipolar disorder. Despite the small sample size and open-label study design, the rapid onset of adjunct effect in the subjects who responded to the acetylsalicylic acid is encouraging as this could prove useful for encouraging compliance and reducing suicide risk.

Nery et al. (2008) studied 28 patients with bipolar affective disorder (DSM-IV) currently in a depressive or mixed state, who had been on a mood stabilizer or atypical antipsychotic for 4 weeks without improvement. Subjects were matched for age, sex, race, baseline HDRS score, baseline Young Mania Rating Score, age at onset, comorbid disorders, and comedication. Patients were randomised to placebo or celecoxib 400mg/day and followed up for six weeks. 23 patients completed the trial. There was a statistically significant reduction in HDRS score in celecoxib group compared to placebo group at week 1 ($p=0.028$), in the subset of patients who completed 6 weeks of the trial, but not in any other week.

Akhondzadeh et al. 2009 studied 40 outpatients with major depression (DSM-IV-TR). Patients were matched for sex, age, previous episodes and previous medications. The study period was 6 weeks. Patients were randomised to fluoxetine (20mg/day for first two weeks, thereafter 40mg/day) and celecoxib 400mg/day, or fluoxetine plus placebo. The patients were free of all psychotropic medications for 4 weeks before the study. Both groups showed a significant improvement in HDRS scores at 6 weeks. A significant ($p<0.02$)

difference was observed in the change in scores between the two groups at the end point. There was no significant difference between groups in the side effects which were monitored over the trial period; nor in plasma fluoxetine levels between celecoxib and placebo groups at weeks 4 and 6. However, the trial did not account for duration of current episode or age of onset in matching patients in the two groups; patients with more recent onset of depression might be expected to do better.

Proposition for a large multicentre trial

We propose a study which will expand this preliminary work in several ways: firstly, we will use celecoxib as an adjunct to the commonly prescribed SSRI citalopram, recommended by NICE as first-line monotherapy for depression due to its favourable side effect profile (NICE guidance CG90 2009); secondly, by enrolling a larger number of participants, we will increase the power of our study; thirdly, we will study the effects of adjunctive celecoxib in a primary care population, as the majority of patients with depression are treated in this setting so our results will be applicable to a larger population; fourthly, we will follow up our patients for a longer period of time, six months, to determine whether they achieve remission.

Objectives

- To determine whether citalopram plus celecoxib dual therapy achieves a greater reduction in depressive symptoms (HDRS score) (NICE Guidelines 2009) within four weeks, compared to citalopram monotherapy.
- To determine whether citalopram plus celecoxib dual therapy is more likely to achieve remission (HDRS score ≤ 7) of moderate to severe depression within six months, compared with citalopram monotherapy.

Endpoints

- HDRS (Nery et al. 2008) score after six months of treatment.
- Reduction in HDRS (Nery et al. 2008) score after four weeks of treatment.

Study design

The study will enrol 452 participants from general practices who have a moderate or severe, current or recurrent major depressive episode when medication with an SSRI is considered. Major depression is diagnosed by the Mini International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al. 1998), and severity of depression is determined using the Hamilton Depression Rating Scale (HDRS) (NICE Guidelines 2009). The patient's general practitioner (GP) will carry out this initial assessment, ensure that the patient meets the inclusion criteria for the study and check the patient's

blood pressure. The British National Formulary (BNF) 58 recommends that all patients have their blood pressure checked before commencing celecoxib therapy.

The study population will be stratified according to age, sex, HDRS score, age at onset of first episode, number of previous depressive episodes and duration of current episode. The patients will then be randomised into two groups of equal size by an independent administrator, using the RAND function of Microsoft Excel. Both the patient and clinicians will be masked. Patients in one group will take citalopram 20mg once daily plus celecoxib 400mg (200mg twice daily); patients in the other group will take citalopram 20mg once daily plus placebo twice daily. The drugs should be supplied in appropriately blinded packaging.

Hospital pharmacies will be informed of each patient's group allocation asked to prepare and dispense the appropriate prescriptions for each patient.

Each subject should be given a diary to record missed doses, side-effects and any suicidal feelings on each day of the study. These will then be reviewed anonymously to ensure adequate compliance (>90% doses taken) and need for intervention for suicidal symptoms. Pill counts at each appointment will also allow us to measure compliance.

The patients will attend an appointment with an investigating psychiatrist at week 0, week 1, week 2, week 3 and week 4. At each appointment, the psychiatrist will determine the patient's HDRS score, ask about side-effects from the treatment, and check the patient's blood pressure. This method of assessment will reduce the inter-clinician variability which could confound the HDRS results if all the GPs who recruited patients used the rating scale individually. At the week 2 and week 4 appointments, a blood sample will be taken to measure plasma citalopram levels, to exclude the possibility of a pharmacokinetic interaction between citalopram and celecoxib increasing the bioavailability of citalopram. The week 4 HDRS scores will be compared between the celecoxib and placebo group.

The initial dose of citalopram 20mg once daily may not be sufficient to improve symptoms in some patients. The BNF58 recommends increasing the dose in increments of 20mg, to a maximum dose of 60mg daily. At the week 4 appointment, the reviewing psychiatrist may increase the citalopram dose to 40mg once daily if the patients' HDRS score has not decreased. The interim data will be analysed to determine whether there is a significant difference between the HDRS score decrease in the two groups. We recognise that the doses of citalopram in the celecoxib and placebo groups must be the same to permit meaningful analysis of the efficacy of celecoxib as an adjunct; however we also feel that denying symptomatic patients an increase in citalopram dose where clinically indicated cannot be justified ethically.

The patients will also be reviewed by the psychiatrist at week 8. If there is still no improvement in

HDRS score, the dose of citalopram may be increased to 60mg. Thereafter the patients will be reviewed at week 12, week 16 and week 20 by the investigating psychiatrist. The HDRS score, blood pressure and any side-effects will be recorded.

The final review at week 26 will be carried out by an investigating psychiatrist. The HDRS score, BP and side-effects experienced will be recorded. The final HDRS scores will be analysed to determine whether there is a significant difference in the number of patients achieving remission in each group.

The trial will end for each subject at their final review after 26 weeks of pharmacotherapy, upon which they will revert to a current standard of care (citalopram monotherapy under the supervision of their general practitioner).

The primary end point is the HDRS score 26 weeks after beginning pharmacotherapy. The secondary endpoint is the HDRS score 4 weeks after beginning pharmacotherapy.

Inclusion and exclusion criteria

Table 1. Inclusion Criteria

Current or recurrent major depressive episode	Determined using M.I.N.I.
Moderate or severe depressive episode	Hamilton Depression Rating Scale score ≥ 18
Age	≥ 18

Table 2. Exclusion Criteria

Contraindications to Celecoxib(BNF58)	History of cerebrovascular disease Ischaemic Heart Disease Peripheral arterial disease Moderate to severe heart failure Previous upper GI haemorrhage
Co-morbidities	Other psychiatric diagnoses, including bipolar affective disorder, post-traumatic stress disorder, generalised anxiety disorder, borderline personality disorder and obsessive-compulsive disorder (detected by M.I.N.I.) Other medical comorbidities Comedication
Contraindications to citalopram (BNF58)	Epilepsy Cardiac Disease Diabetes mellitus
Others	Significant suicidal ideation Enrolment in another trial concurrently Relationship to investigators Concurrent psychotherapy or cognitive behavioural therapy

Adverse events

SSRIs and NSAIDs both increase the risk of upper GI haemorrhage (Paton et al. 2005). There are no studies examining whether co-administration of citalopram and NSAIDs puts patients at greater risk than administering these drugs separately; a recent large trial demonstrated no excess risk of gastric bleeding with co-administration of NSAIDs with fluoxetine (Targownik 2009). Celecoxib is a selective COX-2 inhibitor: these drugs carry a lower risk of serious upper GI side effects than the non-selective COX inhibitors. If any patient suffers an upper GI haemorrhage, this must be reported and the patient must be withdrawn from the trial.

Selective COX-2 inhibitors increase the risk of thrombotic events (myocardial infarction, stroke). Patients with a history of cerebrovascular or ischaemic heart disease will be excluded from the study. Nevertheless any patient who suffers a thrombotic event during the study must be withdrawn, and the event reported.

Ethical considerations

This study will involve patients and therefore ethical committee approval will be essential. Both drugs have been in use clinically for some time and have well characterised contraindications which have been incorporated into the exclusion criteria.

A precedent for co-administration also exists in the pilot studies with no adverse effects attributable, however these report only small sample sizes and so the level and nature of risk should be appropriately communicated to patients at the time of consent.

This investigation is highly relevant: if celecoxib should be demonstrated as an effective, quick acting adjunct, many patients would benefit in the future. We have aimed from the outset to be rigorous in our approach to avoid unnecessary risk to either individuals the population.

Conclusion

Using NSAIDs as an adjunct to antidepressant therapy is an exciting new development, underpinned by an expanding body of biological research. The proposed trial recruits more subjects and is higher-powered than previous trials, as well as having a longer follow-up period. NSAIDs have been in clinical use for many years and may represent a fast-acting treatment acceptable to many patients and doctors.

References

1. Akhondzadeh S, Jafari S, Raisi F, Nasehi AA, Ghoreishi A, Salehi B, et al. Clinical trial of adjunctive celecoxib treatment in patients with major depression: a double blind and placebo controlled trial. *Depress Anxiety* 2009; 26:607-11.
2. Berk M, Wade AA, Kuschke RH, O'Neill-Kerr A. Acute phase proteins in major depression. *J Psychosom Res* 1997; 43:529-34.
3. Collantes-Estevez E, Fernandez-Perez C. Improved control of osteoarthritis pain and self-reported health status in non-responders to celecoxib switched to rofecoxib: results of PAVIA, an open-label post-marketing survey in Spain. *Curr Med Res Opin* 2003; 19:402-10.
4. Excellence NIfC. Depression in Adults. NICE Guidelines 2009; 90.
5. Hedlund E. *J Operational Psych* 1979; 10:149-165.
6. Mendlewicz J, Kriwin P, Oswald P, Souery D, Alboni S, Brunello N. Shortened onset of action of antidepressants in major depression using acetylsalicylic acid augmentation: a pilot open-label study. *Int Clin Psychopharmacol* 2006; 21:227-31.
7. 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. *Mol Psychiatry* 2006; 11:680-4.
8. Nemeroff CB, Vale WW. The neurobiology of depression: inroads to treatment and new drug discovery. *J Clin Psychiatry* 2005; 66 Suppl 7:5-13.
9. Nery FG, Monkul ES, Hatch JP, Fonseca M, Zunta-Soares GB, Frey BN, et al. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. *Hum Psychopharmacol* 2008; 23:87-94.
10. Ohishi K, Ueno R, Nishino S, Sakai T, Hayaishi O. Increased level of salivary prostaglandins in patients with major depression. *Biol Psychiatry* 1988; 23:326-34.
11. Paton C, Ferrer IN. SSRIs and gastrointestinal bleeding. *BMJ* 2005; 331(7516):529-30.
12. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol* 2006; 27:24-31.
13. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; 59 Suppl 20:22-33;quiz 34-57.
14. Targownik LE, Bolton JM, Metge CJ, Leung S, Sareen J. Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. *Am J Gastroenterol* 2009; 104:1475-82.

Correspondence:

Mark Agius, MD
SEPT at Weller Wing, Bedford Hospital
Bedford, Bedfordshire, MK42 9DJ, UK
E-mail: ma393@cam.ac.uk