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1. Title Page

Pilot study of treatment of depression in refractory asthma

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Chief Investigator: Professor Liam Heaney, Respiratory Consultant.

Design: The study was a 12 week double blind randomised placebo controlled pilot study to examine the effect on refractory asthma and depression when patients were treated with a selective serotonin reuptake inhibitor (SSRI), (Citalopram 20-40mgs).

The first patient was enrolled on the 4th November 2011 and the last patient completed November 2012.

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2. Abstract

Design

The study was a 12 week double blind randomised placebo controlled feasibility study to examine the effect on refractory asthma and depression when patients were treated with a selective serotonin reuptake inhibitor (SSRI), (Citalopram 20-40mgs). Patients were recruited from the Northern Ireland Regional Difficult Asthma Service in the Belfast Health and Social Care Trust, which is a tertiary referral centre. Due to recruitment difficulties discussed below a second site at the Difficult Asthma Clinic in Heartlands Hospital Birmingham was added at a later date.

Inclusion criteria were refractory asthma, Hospital Anxiety and Depression Scale Score (HADS) ≥11, Hamilton Depression Rating Scale >17. Exclusion criteria were prescription filling of ≤50% of inhaled combination therapy (poor adherence), significant co-morbidity, anti-depressant medication in previous 6 months.

At the Belfast site 239 patients (157 [66%] female, 82 [34%] male) were screened / re-screened at each clinic attendance;

In total from both sites, there were 5 patients (4 Female) in the placebo group and 8 in the citalopram group, (6 Female).

At 12 weeks there were no statistically significant differences between the placebo and Citalopram group for any of the Primary or Secondary outcome measures except for FEV_1 /FVC, which showed improvement in the placebo group (FEV_1 /FVC Placebo 71.2 ± 7.8, Citalopram 60.0± 10.9- p=0.05) and is of no clinical significance.

3. Study Objectives

To identify if treating depression using a selective serotonin reuptake inhibitor (SSRI), Citalopram in subjects with well characterised refractory asthma would improve depression and asthma control.

To generate some pilot data to estimate the numbers required for a multi-centre study and if there was a rationale for taking this forward

4. Study Design and Description

The treatment period was 12 weeks with outcomes (primary and secondary) assessed at baseline and in the final week of treatment.

All patients were assessed for the intervention study using our well established systematic evaluation protocol. Refractory asthma defined as:

1. Persisting symptoms **due to asthma** (ACS >3) despite detailed assessment and management (non-adherence, alternative diagnoses and co-morbidities etc);
2. Minimal maintenance therapy of high dose inhaled steroids ($\geq$ 800 μg BDP or equivalent) long acting β_2-agonist and / or other maintenance therapies (theophylline / leukotriene receptor antagonist).
3. The requirement for maintenance oral steroids for ≥50% of the year or at least 3 courses of systemic steroids in the preceding 12 months.

Inclusion criteria
Age 18-65 years
Refractory asthma
Agreement to take part in trial and to take anti-depressant medication
Hospital Anxiety and Depression Score ≥11
Hamilton Depression Rating Scale ≥ 17

Exclusion criteria
Poor adherence with medication (prescription records, ≤50% of inhaled combination filled in previous 6 months)
Significant co-morbidity due to conditions other than asthma
Anti-depressant medication in previous 3 months
Pregnancy
An MHRA drug safety alert regarding citalopram issued in December 2011 recommended some further contraindications and warnings regarding QT interval prolongation, which required a change to the original protocol exclusion criteria and follow up monitoring, described below:

Patients requiring non-steroidal anti-inflammatory drugs, aspirin or warfarin
Patients with reduced hepatic function

Patients with any history of cardiac disease

Patients with congenital long QT syndrome or known pre-existing QT interval prolongation taking other medicines known to prolong QT interval.

Patients with pre-existing risk factors for QT interval prolongation, including patients with significant bradycardia, recent acute myocardial infarction or decompensated heart failure.

Patients with electrolyte disturbances (eg, hypokalaemia and hypomagnesaemia).

Citalopram may have an additive effect to other drugs that prolong the QT interval. Co-administration of Citalopram with medicines that prolong the QT interval is therefore contraindicated. These include:

- class IA and III antiarrhythmics (eg, amiodarone, dronedarone, quinidine)
- antipsychotics (eg, fentiazine derviatives, pimozide, haloperidol)
- tricyclic antidepressants
- some antimicrobial agents (eg, sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, antimalaria treatment—particularly halofantrine)
- some antihistamines (astemizole, mizolastine)
- some antiretrovirals (eg, ritonavir, saquinavir, lopinavir)

Patients taking concomitant medications known to increase plasma levels of citalopram such as:

- some antiretroviral medications
- omeprazole
- cimetidine.

Primary Outcome measure

To measure improvement in depression and asthma two outcomes will be assessed:

1. Improvement in Asthma Control Score(ACS)
2. Improvement in Hamilton Rating Scale for Depression (HDRS)

Secondary outcome measures

Improvement in Asthma Quality of Life Questionnaire (AQLQ)
Improvement in Hospital Anxiety and Depression Scale (HADS)
Improvement in Lung function
Reduction in Fractional exhaled nitric oxide
Sputum eosinophil count
Reduction in dose of oral steroids (if applicable)

Screening

Refractory Asthma Subjects attending Difficult Asthma Clinic Belfast City Hospital
HADS ≥ 11
Electrocardiogram
Urea and electrolytes including serum magnesium
Liver function tests
Concomitant medication review

Run-in

1. Review of inclusion / exclusion criteria.
2. Informed consent to take part in trial and agreement to take anti-depressant medication.
3. Hamilton Rating Scale for Depression.

If Hamilton Rating Scale for Depression, ≥ 17 proceed to Baseline assessments and randomisation

Randomisation and allocation

Patients were randomly allocated to either the intervention or control group. Patients in the intervention group were commenced on Citalopram 20mgs with the option of increasing to 40 mg after 6 weeks if there was no response. The control group received a matched placebo.

Follow up

Monitoring recommendations:

Monitoring of serum magnesium is advised, particularly in elderly patients, who may be taking diuretics or proton pump inhibitors

If cardiovascular symptoms, such as palpitations, vertigo, syncope, or seizures develop during treatment, cardiac evaluation including an ECG should be undertaken to exclude a possible malignant cardiac arrhythmia.

- If QTc interval is >500 milliseconds, treatment should be withdrawn gradually.
- If QTc interval duration is between 480 milliseconds and 500 milliseconds, the balance of benefits and risks of continued treatment should be carefully considered, alongside options for dose reduction or gradual withdrawal

At **week 4** patients in both groups were assessed for response to treatment (clinical judgement and/or ≥ 50% change in HDRS). If no response, dose (placebo or Citalopram) was increased to 40mgs for the remaining 8 weeks of the study. Patients who responded remained on 20mgs for the remaining 8 weeks.

All patients were contacted 1 week after randomisation and commencing treatment and 1 week after subsequent dose increase to ensure there was no suggestion of agitation or suicidal ideation after commencement of Citalopram / placebo (in accordance with the Guidelines for initiation of SSRI therapy in adults).

Run out- Post study

At the final study visit all participants were assessed by an independent physician who liaised with pharmacy to access the randomisation code and prescribed treatment. Medication withdrawal will be in line with NICE guidelines

Patients on placebo were assessed by the independent physician, informed of placebo treatment, and treatment discontinued. They were referred to GP or clinical

psychologist for ongoing management of their depressive symptoms.

Patients taking Citalopram (40mg / 20 mg) who did not respond were assessed by the independent physician and the dose of Citalopram titrated down and discontinued after 4 weeks. They were referred to GP or clinical psychologist for ongoing management of their depressive symptoms.

Patients taking Citalporam (40mg / 20mg) who responded were informed of specific drug treatment, provided with follow on treatment for 28 days and referred to GP for on-going management

5. Study Results

Data analysis

Data were coded and analyzed using a Statistical Package for Social Sciences (SPSS), Version 16. Descriptive statistics (mean, SD, SE or median, range) and Chi-squared tests were used to summarize patient demographics. In cases where the expected frequency fell below 5 the Fisher's exact test was used. Paired analysis of group means was used to measure change in secondary outcomes in both study groups.

Results

At the Belfast site 239 patients (157 [66%] female, 82 [34%] male) were screened / re-screened at each clinic attendance;

Table 1: Exclusions

Reason	Number
HADS <11	109
Age	16
Anti-depressant	68
Attending Clinical psychology	5
Co-morbidity as per exclusion criteria	4
Non-adherent to medication	4
Not refractory asthma	5
Pregnant or trying to conceive	3
Refused study participation	13
TOTAL	**227**

In total 17 subjects were recruited, 12 at the Belfast site and 5 at the Birmingham site. One patient in Belfast withdrew and 3 in Birmingham with 13 completing the study and included in the analysis.

One of the main reasons for low recruitment was of 239 screened in Belfast, 68 patients (28%) were already prescribed SSRI's – this was a much higher percentage than would have been expected and higher than our previous data (Conway E, Kelly

C, Gamble J, Heaney LG. Prevalence of psychiatric morbidity in difficult asthma: relationship to asthma outcome. Respiratory Medicine 2005 Sep; 99(9):1152-9). Of interest, this prescribing of SSRIs is significantly more common in women and more importantly, depression scores on HADS remained high in a substantial number of patients, suggesting a minimal impact from SSRIs in this population.

Table 2: Patients already prescribed SSRI's

	Female	**Male**	**p value**
Anti-depressant (68 patients)	55 (23%)	13 (6%)	0.02

Table 3: Patients prescribed SSRI's (68) HADs Scores

HADS	**Number (%)**
Anxiety score ≥11	43 (63)
Depression score ≥11	42 (62)
Anxiety OR Depression score ≥11	49 (72)
Anxiety AND Depression score ≥11	35 (51)

Intervention study results

There were 5 patients (4 Female) in the placebo group and 8 in the citalopram group, (6 Female). One of the main reasons for low recruitment as discussed above was the issue of patients already prescribed SSRI's (28%).

Table 4: Baseline Demographics

Demographics	**GROUPS**		
	Placebo n=5	**Citalopram** n=8	**p value**
Female (%)	4 (80%)	6 (75%)	1.0
Age	46.2 ± 6.2	44.0 ± 10.0	0.7
Hosp admissions (range)	0-0	0-1	0.4
Prednisolone Dose	13.5 ± 7.0	13.8 ± 13.3	1.0
Rescue Prednisolone courses	.80 ± 1.1	2.0 ± 2.0	0.2
FeNO	41.8 ± 25.8	22.7 ± 18.6	0.2

HADS Anxiety	13.0 ± 3.5	13.1 ± 2.7	0.9
HADS Depression	10.6 ± 1.1	12.0 ± 2.3	0.2
HDRS	32.2 ± 3.4	31.9 ± 4.9	0.9
ACS	3.8 ± 0.7	4.0 ± 0.8	1.0
AQLQ symptoms	2.2 ± 0.2	2.4 ± 0.8	0.6
AQLQ activity	2.8 ± 0.7	2.9 ± 0.9	0.7
AQLQ emotions	2.0 ± 0.9	2.6 ± 1.3	0.4
AQLQ environment	4.0 ± 1.5	3.4 ± 1.3	0.5
AQLQ Total	2.5 ± 0.8	2.7 ± 0.8	0.7
FEV_1 (l)	1.8 ± 0.4	1.6 ± 0.5	0.5
FEV_1%	70.0 ± 11.5	64.1 ± 19.6	0.6
FVC (l)	2.7 ± 0.5	2.7 ± 0.8	0.9
FVC %	81.0 ± 10.1	83.0 ± 17. 5	0.8
FEV1/FVC	68.8 ± 3.2	62.0 ± 14.4	0.3
Sputum eosinophils	82.7 ± 83.5	35.2 ± 34.9	0.3

Data are presented as mean ± SD unless otherwise stated

There were no statistically significant differences between the groups at baseline.

Table 5: 12 week between Group results

Outcomes	**GROUPS**			
	Placebo n=5	**Citalopram** n=8	**p value**	**CI**
Hosp admissions (range)	0 - 0	0 - 1	0.2	
Prednisolone dose	12.0 ± 6.0	10.6 ± 10.8	0.8	-9.4 – 12.2
Rescue Prednisolone courses	0.8± 0.8	1.3 ± 1.0	0.4	-1.6 - 0 .7
FeNO	59.4 ± 43.3	27.0 ± 28.6	0.2	-20.7 – 85.4
HADS Anxiety	12.6 ± 4.0	9.6 ± 4.0	0.2	-2.2 - 8.1
HADS Depression	10.2 ± 1.9	8.5 ± 2.0	0.2	-.85 – 4.3
HDRS	24.8 ± 7.7	16.0 ± 4.3	0.06	-.61 – 18.2
ACS	3.8 ± 0.9	3.5 ± 0.9	0.6	-.85 – 1.2
AQLQ symptoms	2.7 ± 0.4	2.7 ± 0.8	0.9	-8.1 – 0.7
AQLQ activity	2.7± 0.6	3.3 ± 0.8	0.2	-1.4 – 0.3
AQLQ emotions	2.4 ± 0.9	3.1 ± 0.7	0.1	-1.8 – 0.3
AQLQ environment	3.2 ± 0.8	4.4 ± 1.2	0.07	-2.5 – 0.1
AQLQ Total	2.7 ± 0.5	3.2 ± 0.5	0.1	-1.1 – 0.1
FEV_1 (l)	2.1 ± 0.5	1.6 ± 0.4	0.09	-0.1 – 1.1
FEV_1%	80.8 ± 11.5	63.4 ± 17.5	0.07	-1.9 – 36.7
FVC (l)	3.0 ± 0.4	2.7 ± 0.8	0.5	-4.9 – 1.0
FVC %	90.8 ± 11.7	84.6 ± 18.2	0.5	-12.1 – 24.4

FEV_1/FVC	71.2 ± 7.8	60.0± 10.9	*0.05	-0.2 – 22.6
Sputum eosinophils	29.0 ± 18.3	38.3 ± 59.6	0.8	-140.4 – 121.8

Data are presented as mean ± SD unless otherwise stated
*Significance at the 0.05 level

At 12 weeks there were no statistically significant differences between the placebo and Citalopram group for any of the outcomes measures except for FEV_1 /FVC, which showed improvement in the placebo group (**Table 5).**

Table 6: 12 weeks within citalopram group results

Outcomes	**Citalopram Group (n=8)**			
	Baseline Pre-Citalopram	**12 weeks Post-Citalopram**	**p value**	**CI**
Hosp admissions (range)	0 - 1	0 - 1	0.3	
Prednisolone dose	13.8 ± 13.2	10.6 ± 10.8	0.2	-1.8 – 8.1
Rescue Prednisolone courses	2.0 ± 2.0	1.3 ± 1.0	0.1	-0.3– 1.8
FeNO	22.7 ± 18.6	29.7 ± 29.7	0.2	-20.2 – 6.2
HADS Anxiety	13.1 ± 2.7	9.6 ± 3.9	*0.02	0.8 – 6.2
HADS Depression	12.0 ± 2.3	8.5 ± 2.0	*0.01	1.3 – 5.7
HDRS	31.9 ± 4.9	16.0 ± 4.3	*0.00	11.1 – 20.6
ACS	4.1 ± 0.7	3.5 ± 0.9	0.07	-0.1 – 1.2
AQLQ symptoms	2.4 ± 0.8	2.7 ± 0.8	0.4	-1.1 - 0 .5
AQLQ activity	2.9 ± 0.9	3.3 ± 0.8	.1	-0.9 - 0 .1
AQLQ emotions	2.6 ± 1.3	3.1 ± 0.7	0.3	-1.6 - 0 .5
AQLQ environment	3.4 ± 1.3	4.4 ± 1.2	*0.01	-1.7 - -0.3
AQLQ Total	2.7 ± 0.8	3.2 ± 0.5	0.07	-1.1 - 0 .1
FEV_1 (l)	1.6 ± 0.5	1.6 ± 0.4	0.7	-0.2 - 0 .2
FEV_1%	64.1 ± 19.6	63.4 ± 17.5	0.8	-7.0 – 8.4
FVC (l)	2.7 ± 0.8	2.7 ± 0.8	0.7	-0.3 - 0 .2
FVC %	83.0 ± 17.4	84.6 ± 18.1	0.6	-9.1 – 5.9
FEV_1/FVC	62.0 ± 14.4	60.0 ± 10.9	0.4	-3.3 – 7.3
Sputum eosinophils	35.0 ± 49.5	53.5 ± 75.6	0.5	-253.6 – 216.6

Data are presented as mean ± SD unless otherwise stated
*Significance at the 0.05 level

There were as would be expected statistically significant differences within the

Citalopram group between baseline and 12 weeks, with regards to improvements in HADs anxiety and depression scores, and HDRS scores. Improvement was also noted in the AQLQ environment score and a trend towards significance in the AQLQ total score.

Table 7: 12 weeks within placebo group results

Outcomes	Placebo Group (n=5)			
	Baseline Pre-Placebo	**12 weeks Post-Placebo**	**p value**	**CI**
Hosp admissions (range)	0 - 0	0 - 0	1.0	
Prednisolone dose	13.5 ± 7.0	12.0 ± 7.0	0.2	-1.3 – 4.3
Rescue Prednisolone courses	0.8 ± 1.1	0.8 ± 0.8	1.0	-0.9 - 0 .9
FeNO	41.8 ± 25.9	59.4 ± 43.3	0.3	-58.5 – 23.3
HADS Anxiety	13.0 ± 3.5	12.6 ± 4.0	0.6	-1.5 – 2.3
HADS Depression	10.6 ± 1.1	10.2 ± 1.9	0.7	-2.5 – 3.3
HDRS	32.2 ± 3.4	24.8 ± 7.7	0.2	-4.8 – 19.6
ACS	4.1 ± 0.7	3.8 ± 0.9	0.6	-1.1 – 1.6
AQLQ symptoms	2.2 ± 0.6	2.7 ± 0.4	0.1	-1.1 - 0.2
AQLQ activity	2.8 ± 0.7	2.7 ± 0.6	1.0	-1.3 – 1.3
AQLQ emotions	2.0 ± 1.0	2.4 ± 0.9	0.2	-1.0 - 0.2
AQLQ environment	4.0 ± 1.5	3.2 ± 0.8	0.3	-0.9 – 2.3
AQLQ Total	2.5 ± 0.7	3.2 ± 0.5	0.6	-1.1 - .7
FEV_1 (l)	1.8 ± 0.4	2.1 ± 0.5	0.2	-0.9 - 0 .3
FEV_1%	70.0 ± 11.5	70.0 ± 13.7	0.2	-33.3 – 11.7
FVC (l)	2.7 ± 0.5	3.0 ± 0.4	0.7	-0.9 -0 .2
FVC %	81.0 ± 10.1	90.8 ± 11.7	0.2	-28.9 – 9.3
FEV_1/FVC	68.8 ± 3.2	71.2 ± 7.8	0.5	-10.7 – 5.9
Sputum eosinophils	35.5 ± 24.7	29.0± 18.4	0.4	-50.7 – 63.7

Data are presented as mean ± SD unless otherwise stated
*Significance at the 0.05 level

There were no statistically significant differences found within the placebo group between baseline and 12 weeks.

6. Safety Evaluation

There were no Adverse Events, Serious Adverse events or Other Significant Adverse Events reported during the study period.

7. Discussion and conclusion

The level of depression identified is very high and much higher than we measured some years ago reflecting the much more widespread use of this medication in depression in primary care. However the data does support the previous work which reported a high level of psychiatric morbidity in this population and can conclude that this score remains abnormal in many subjects on this class of medication. Of interest, and which we believe to be important is the fact that this prescribing of SSRIs is significantly more common in women (55 of the 68 were female, $p<0.02$). More importantly, depression scores using the Hospital Anxiety and Depression Score remained high in a substantial number of patients, despite being on an SSRI, suggesting a minimal impact from SSRIs in this population. This supports further examination of other strategies in this population.

In terms of feasibility, we encountered multiple issues with this work. All of these issues have been beyond our control and had the effect of introducing a delay in study completion.

The substantive feasibility issues in brief were:

- 12 month delay from the initial application for sponsorship to the Belfast Trust Research and Development Department in December 2009, until the first patient was recruited into the study in November 2010;

- substantial number of patients already on SSRI at time of referral which affected recruitment

- an MHRA drug safety alert regarding citalopram issued in December 2011 recommended some contraindications and warnings regarding QT interval prolongation, which required a change to the current protocol exclusion criteria and follow up monitoring. A concomitant MHRA amendment was submitted and approved. The issue of the alert further reduced the probability of recruiting patients as a large percentage of patients with refractory asthma are prescribed proton pump inhibitors such as omeprazole, which was one of the contra-indicated medications known to increase plasma levels of citalopram.

We have managed these issues effectively, but there was a resultant delay. Asthma UK were made aware of these and granted at our request, a study extension until 31st January 2013.

We did hope to establish pilot data for a larger study, but due to the widespread SSRI prescribing and the recent MHRA guidance as discussed above, this study can probably not be done in the UK currently.