Mecamylamine in the Treatment of Depressed Patients who were Inadequate Responders to Citalopram First-line Therapy; a Double-blind Placebo Controlled Add-on Study

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Introduction

The STAR*D study reminds us of the poor remission rate (28%) seen after first-line treatment for depression. Considering currently available antidepressants, antagonism at the neuronal nicotinic receptors (NNRs) in the brain, may be an important part of their pharmacology (Shytle et al, 2002). That NNRs are relevant to the expression of an antidepressant effect has been shown in animals. Knockout mice with no NNR β2 subunit did not respond to amitriptyline in 3 animal models of depression, when compared to wild-type mice (Caldarone et al, 2004). Mecamylamine is an NNR antagonist which has been marketed in the USA for the treatment of hypertension. Typical antihypertensive doses are 25-90mg daily in divided doses. Lower doses in the range 2.5-10 mg have no hypotensive effects but still antagonize CNS located NNRs. A study in Tourette's disorder showed no benefit on tics but a meaningful reduction in sudden mood swings and symptoms of depression (Silver et al, 2001).

Objectives

The primary objectives of the study were (1) to assess the effectiveness of mecamylamine as an antidepressant when added to citalopram treatment in subjects who were inadequate responders to first line therapy and (2) to assess the safety and tolerability of mecamylamine as add-on treatment to citalopram.

Methodology

Patients

Male or female subjects aged 18 -70 were recruited from outpatient facilities located in either a general or psychiatric hospital. Nine (9) centers were used, 1 in the USA and 8 in India. After giving written informed consent, subjects who met DSM IV criteria for Major Depressive Disorder (MDD), had a Hamilton Depression Rating Scale -17 items (HAMD-17) score >21 and a Clinical Global Impression – Severity of Illness (CGI-SI) score greater than or equal to 4 were eligible for the study

Dosing

Included subjects had a 3-5 day washout period during which baseline evaluations were obtained and any psychotropic medication gradually withdrawn. Subjects were then started on citalopram in an open label fashion. Citalopram therapy started at 20 mg once daily and monotherapy lasted 6 weeks. During this period, citalopram could be increased at Week 2 to 40 mg once daily, if considered appropriate by the investigator. After 6 weeks open citalopram treatment, subjects were assessed using the HAMD-17 rating scale and those with a score greater than or equal to 14, plus a CGI-SI score of greater than or equal to 4, were considered inadequate responders and were randomized to receive either placebo or mecamylamine as an add-on to continued citalopram therapy. Mecamylamine was started at 5 mg daily. After 2 weeks treatment, medication could be increased to 7.5 mg or continued unchanged. After a further 2 weeks, medication could be increased to 10 mg if felt appropriate by the investigator. At any time during the last 6 weeks of the double-blind phase of the study, placebo or mecamylamine could be reduced to the previous dose level following the emergence of any adverse event.

Outcome Measures

The primary outcome measure was the change from baseline (week 6) to week 14 on the HAMD-17 scale. Secondary measures included the Montgomery Asberg Depression Rating Scale (MADRS), the CGI-SI and CGI global change scores (CGI-GC), the Sheehan Irritability (SIS) and Disability (SDS) scales.

Statistics

All analyses were carried out using SAS (Version 9.02). Continuous variables were analyzed using an ANOVA model while categorical data was assessed using the chi-squared test. The ANOVA was carried out using SAS PROC GLM and the terms of the model included treatment, baseline score, pooled sites and education level. The primary efficacy analysis involved the Per Protocol (PP) study population and included subjects who completed the double blind phase of the trial, had no major protocol violations and were at least 80% compliant with study medication. The Intent to Treat (ITT) population included all subjects randomized into the double blind phase of the trial and who had at least one dose of study medication. The safety analysis used the ITT population. In the ITT efficacy analysis, missing data were handled using a Last Observation Carried Forward (LOCF) technique.

Summary of Baseline Demographics

Characteristic	Entering Open Label Phase	Treatment (ITT Population)		
		Placebo	Mecamylamine	Total
N	**450**	**92**	**92**	**184**
Gender: **Male** **Female**	 224 (50%) 226 (50%)	 44 (48%) 48 (52%)	 40 (43%) 52 (57%)	 84 (46%) 100 (54%)
Race: **Asian** **Black** **Hispanic** **White**	432 (96%) 2 (0%) 0 (0%) 16 (4%) 2 (0%) 0 (0%) 16 (4%)	89 (97%) 0 (0%) 0 (10%) 3 (3%)	87 (95%) 0 (0%) 0 (0%) 5 (5%)	176 (96%) 0 (0%) 0 (0%) 8 (4%)
Age (yr) mean **S.D**	36.2 11.53	34.1 9.67	36.1 10.76	35.1 10.25

Summary of Baseline Efficacy Measures

Variable	Statistics	Placebo (n=92)	Mecamylamine (n=92)
HAMD-17 Total Score	Mean (SD)	20.5 (4.18)	20.7 (4.43)
CGI-Severity Score	Mean (SD)	4 (0.31)	4 (0.29)
MADRS Total Score	Mean (SD)	25.8 (5.34)	26.6 (6.17)

Change from Baseline to Endpoint on the Hamilton Depression Scale

HAMD-17 Total			
Variable	**Placebo**	**Mecamylamine**	**p-value**
PP Population	**n=74**	**n=77**	
Mean Baseline (SD)	20.7(4.10)	20.6 (4.46)	
Mean Change (SD)	-9.7 (8.94)	-11.4 (7.93)	
LS Mean Change (SE)	-10.28 (1.16)	-12.29 (1.22)	
Difference of LS Mean & 95% CL		-2.008 [-4.07, 0.06]	0.059
ITT Population (LOCF)	**n=79**	**n=81**	
Mean Baseline (SD)	20.6 (4.30)	20.6 (4.46)	
Mean Change (SD)	-9.9 (9.34)	-11.7 (8.00)	
LS Mean Change (SE)	-10.14 (1.01)	-12.23 (1.10)	
Difference of LS Mean & 95% CL		-2.090 [-4.07, -0.11]	0.041

Change from Baseline to Endpoint on the Montgomery Asberg Depression Scale

MADRS Total Score			
Variable	**Placebo**	**Mecamylamine**	**p-value**
PP Population	**n=74**	**n=77**	
Mean Baseline (SD)	25.8 (5.07)	26.2 (6.01)	
Mean Change (SD)	-11.8 (10.22)	-15.1 (8.85)	
LS Mean Change (SE)	-11.87 (1.35)	-15.19 (1.39)	
Difference of LS Mean & 95% CL		-3.3153 [-5.69, -0.94]	0.007
ITT Population (LOCF)	**n=90**	**n=92**	
Mean Baseline (SD)	25.7 (5.20)	26.6 (6.17)	
Mean Change (SD)	-11.6 (10.46)	-14.1 (9.38)	
LS Mean Change (SE)	-10.48 (1.26)	-12.57 (1.28)	
Difference of LS Mean & 95% CL		-2.097 [-4.46, 0.26]	0.083

Change from Baseline to Endpoint on the CGI-GC Scale

CGI-GC			
Variable	**Placebo**	**Mecamylamine**	**P-value**
PP Population	**n=74**	**n=77**	
Mean (SD)	2.1 (1.06)	1.7 (0.78)	
LS Mean (SE)	2.03 (0.15)	1.66 (0.16)	
Difference of LS Mean & 95% CL		-0.3716 [-0.65, -0.09]	0.010
ITT Population (LOCF)	**n=90**	**n=92**	
Mean (SD)	2.1 (1.04)	1.9 (0.91)	
LS Mean Change (SE)	2.11 (0.13)	1.89 (0.14)	
Difference of LS Mean & 95% CL		-0.2277 [-0.50, 0.04]	0.101

Change from Baseline to Endpoint on the CGI-SI Scale

CGI- SI			
Variable	**Placebo**	**Mecamylamine**	**P-value**
PP Population	n=74	n=77	
Mean Baseline (SD)	4.1 (0.25)	4.1 (0.22)	
Mean Change (SD)	-1.5 (1.30)	-1.8 (1.12)	
LS Mean Change (SE)	-1.60 (0.19)	-1.96 (0.20)	
Difference of LS Mean & 95% CL		-0.3624 [-0.71, -0.01]	0.043
ITT Population (LOCF)	**n=77**	**n=79**	
Mean Baseline (SD)	4.0 (0.32)	4.0 (0.25)	
Mean Change (SD)	-1.5 (1.27)	-1.8 (1.12)	
LS Mean Change (SE)	-1.59 (0.17)	-1.97 (0.18)	
Difference of LS Mean & 95% CL		-0.3715 [-0.71, -0.03]	0.033

Change from Baseline to Endpoint on the Sheehan Disability Score

SDS Total Score			
Variable	**Placebo**	**Mecamylamine**	**p-value**
PP Population	**n=56**	**n=58**	
Mean Baseline (SD)	12.6 (5.93)	12.8 (4.50)	
Mean Change (SD)	-5.0 (6.33)	-7.5 (5.03)	
LS Mean Change (SE)	-4.50 (0.84)	-7.05 (0.89)	
Difference of LS Mean & 95% CL		-2.5496 [-4.24, -0.86]	0.004
ITT Population (LOCF)	**n=61**	**n=62**	
Mean Baseline (SD)	12.5 (5.90)	12.8 (4.38)	
Mean Change (SD)	-5.2 (6.36)	-7.4 (4.98)	
LS Mean Change (SE)	-4.55 (0.73)	-6.80 (0.80)	
Difference of LS Mean & 95% CL		-2.2491 [-3.87, -0.63]	0.008

Change from Baseline to Endpoint on the Sheehan Irritability Score

SIS Total Score			
Variable	**Placebo**	**Mecamylamine**	**p-value**
PP Population	**n=44**	**n=47**	
Mean Baseline (SD)	23.3 (9.44)	23.8 (8.64)	
Mean Change (SD)	-9.2 (9.77)	-13.9 (10.10)	
LS Mean Change (SE)	-4.13 (1.89)	-9.72 (1.84)	
Difference of LS Mean & 95% CL		-5.5893 [-8.65, -2.53]	<0.001
ITT Population (LOCF)	**n=49**	**n=51**	
Mean Baseline (SD)	23.4 (9.79)	23.8 (8.46)	
Mean Change (SD)	-9.7 (10.38)	-14.0 (10.11)	
LS Mean Change (SE)	-4.11 (1.75)	-9.47 (1.74)	
Difference of LS Mean & 95% CL		-5.3590 [-8.26, -2.45]	<0.001

Discussion

This study suggests mecamylamine add-on treatment improved symptoms of depression in patients who were inadequate responders to first-line citalopram therapy. A statistical advantage was seen on the primary outcome measure (HAMD-17) which was supported by advantages on most of the secondary measures. In particular a strong advantage was seen on the SIS. This scale measures domains of irritability, frustration, edginess, moodiness, anger with self, anger with others and temper. Irritability is a common feature in depression and may not be alleviated by currently available antidepressants. It is possible they may even worsen the irritability. Thus mecamylamine may offer a different therapeutic profile compared to current antidepressant therapies. In this study the combination was safe and well tolerated the most common side-effects due to mecamylamine being constipation and dizziness.

Conclusions

- Mecamylamine was superior to placebo, when added to patients who were inadequate responders to first-line treatment with citalopram
- Mecamylamine was superior to placebo in treating symptoms of irritability. This may be a unique feature in its therapeutic profile.
- In this trial the mecamylamine + citalopram combination was safe and well tolerated
- NNR antagonists like mecamylamine may be an important new therapy for treating this group of patients with high unmet medical need

References

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*Although presently affiliated with Ventureast Pharmaceutical Services , Dr. Kuchibhatla was employed at Targacept while the research supporting this poster was conducted.