

**CLINICAL REVIEW: RELATIONSHIP BETWEEN
ANTIDEPRESSANT DRUGS AND SUICIDALITY IN ADULTS**

Application Type	NDA
Submission Number	Bupropion (018-644) Citalopram (020-822, 021-046) Duloxetine (021-427) Escitalopram (021-323, 021-365) Fluoxetine (018-936, 021520) Fluvoxamine (75-888,021-519) Mirtazapine (020-415) Nefazodone (020-152) Paroxetine (020-031, 20-710, 20-936, 021-299) Sertraline (019-839, 020-990) Venlafaxine (020-151, 020-699)
Reviewers' Names	Marc B. Stone, M.D. M. Lisa Jones, M.D.
Review Completion Date	November 17, 2006
Established Name	Multiple
(Proposed) Trade Name	Multiple
Therapeutic Class	Multiple Antidepressants
Applicant	Multiple
Formulation	Multiple
Dosing Regimen	Multiple
Indication	Multiple
Intended Population	Users of Antidepressant Products

Table 5: Classification of Antidepressant Drugs

Newer Drugs			Older Drugs	
SSRI	SNRI	Other Modern Antidepressants	Tricyclics	Other Antidepressants
Citalopram	Duloxetine	Bupropion	Amitriptyline	Mianserin
Escitalopram	Venlafaxine	Mirtazapine	Clomipramine	Trazodone
Fluoxetine		Nefazodone	Desipramine	
Fluvoxamine			Dothiepin	
Paroxetine			Imipramine	
Sertraline				

Because age is a variable of particular interest due to the association of suicidality with antidepressant use in the pediatric population, analyses were performed using age and the interaction of age with treatment to explore linear or curvilinear relationships between age, treatment and measures of suicidality and treatment efficacy using multivariable fractional polynomial models¹⁵. Extensive categorical analyses of age were also performed (Table 6):

Table 6: Age Categories

	Categories
Young vs. Older Adults	<25, 25+
Young, Middle-aged and Elderly	<25, 25-64, 65+
Age by Decade	<25, 25-34, 35-44, 45-54, 55-64, 65-74, 75+
Age by Double Decade	<25, 25-44, 45-64, 65+

4. RESULTS

4.1 Characteristics of the data

Table 7 shows the number of subjects assigned to drug (as primary drug or active control) and placebo by drug and drug class.

¹⁵ Sauerbrai W and Royston P. Building multivariable prognostic and diagnostic models: transformation of predictors using fractional polynomials. J R Statist. Soc. A 162:71-94.

Table 16: Suicidal Behavior Risk for Active Drug relative to Placebo – Preparation or Worse –Adults with Psychiatric Disorders – By Drug and Drug Class

Drug Class Drug	Odds Ratio	95% Confidence Interval	p value
All Drugs	1.10	0.77 - 1.56	0.60
SSRI	1.23	0.82 - 1.85	0.31
Citalopram	1.97	0.56 – 7.00	0.29
Escitalopram	5.67	0.94 – 34.2	0.06
Fluoxetine	1.08	0.52 – 2.23	0.83
Fluvoxamine	1.31	0.51 – 3.38	0.58
Paroxetine	2.76	1.16 – 6.60	0.02
Sertraline	0.25	0.07 – 0.90	0.03
Equality within class	NA	NA	0.03
SNRI	0.83	0.35 – 1.97	0.68
Duloxetine	1.17	0.18 – 7.53	0.87
Venlafaxine	0.69	0.25 – 1.89	0.46
Equality within class			0.62
Other Modern Antidepressants	0.99	0.46 – 2.10	0.97
Bupropion	2.41	0.48 – 12.1	0.29
Mirtazapine	1.25	0.34 – 4.62	0.73
Nefazodone	0.53	0.15 – 1.82	0.31
Equality within class	NA	NA	0.32
Equality across “Newer” drugs	NA	NA	0.12
Tricyclic Antidepressants	0.80	0.38 – 1.68	0.56
Amitriptyline	0	0 - inf	0.98
Clomipramine	0.77	0.14 – 4.15	0.76
Desipramine	0.83	0.07 – 9.89	0.88
Dothiepin	0	0 - inf	0.98
Imipramine	0.85	0.34 – 2.11	0.73
Equality within class	NA	NA	1.00
Other Antidepressants	1.12	0.10 – 12.8	0.93
Mianserin	1.04	0.09 – 12.2	0.98
Trazodone	-	NA	NA
Equality within class	NA	NA	NA
Equality across “Older” drugs	NA	NA	1.00
Equality across All Drugs	NA	NA	0.44
Equality across All Classes	NA	NA	0.81
Equality across All Trials	NA	NA	1.00

Note: all estimates were obtained using conditional logistic regression
NA – not applicable

Table 18: Suicidal Behavior Risk for Active Drug relative to Placebo – Preparation or Worse –Adults with Psychiatric Disorders – By Age

Age Range	Odds Ratio	95% Confidence Interval	p value
<25	2.30	1.04 – 5.09	0.04
25 - 34	0.81	0.43 – 1.52	0.53
35 - 44	0.89	0.42 – 1.87	0.75
25 – 44	0.88	0.54 – 1.42	0.59
45 - 54	2.29	0.73 – 7.14	0.15
55 - 64	0.89	0.17 – 4.73	0.89
45 – 64	1.75	0.68 – 4.48	0.24
25 – 64	1.03	0.68 – 1.58	0.88
65 – 74	0.09	0.01 – 0.95	0.04
75 +	0	0 - inf	1.00
65+	0.06	0.01 – 0.58	0.01
>24	0.87	0.58 – 1.29	0.48
Tests for equality of effect across age by			
Deciles	NA	NA	0.29
Quintiles	NA	NA	0.20
Quartiles	NA	NA	0.43
Terciles	NA	NA	0.86
<25 vs. 25+			0.04
25 – 34 vs. 35 – 44			0.97
45 – 54 vs. 55 – 64			0.42
25 – 44 vs. 45 – 64			0.86
25 – 64 vs. 65+			0.02

Note: all estimates were obtained using conditional logistic regression
 NA – not applicable