

Study Talk: SSRIs and Self-harm in Borderline Personality Disorder



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Terminology and definitions

- **Self-aggression / self-harm:** Any intentional behavior that has the goal of inflicting harm on ONESELF that has a greater than zero probability of succeeding
- Self-Aggressive thoughts and behaviors
 - **Suicide:** the act of intentionally ending one's own life
 - **Suicide attempt:** engagement in potentially self-injurious behavior in which there is at least some intent to die.
 - **Suicidal ideation:** thoughts of engaging in behavior intended to end one's life
 - **Nonsuicidal self-injury (NSSI) :** self-injury in which a person has no intent to die

Self-harm is a public health problem

- ~ 11 suicide deaths per 100,000 people in US
- 16.9% of high school students in the US seriously considered attempting suicide in past year.
 - 8% attempted suicide one or more times during this same period
- ~ 20% of individuals in US engage in non-suicidal self-injury
- Estimates for lost productivity and medical treatment for all forms of self-injury were in excess of \$33 billion

Borderline Personality Disorder is strongly associated with self-harm

- Borderline Personality Disorder (BPD)
 - Marked by an unstable self-concept and affective dysregulation
 - Prevalence: 2% community, up to 20%-40% psychiatric
- BPD and self-harm
 - 60% - 80% of individuals with BPD engage in NSSI
 - 60% - 75% of individuals with BPD attempt suicide
 - Up to 10% of individuals with BPD commit suicide

BPD is often treated with SSRIs

- BPD associated with affect dysregulation
- BPD co-morbid with Major Depressive Disorder
 - Especially among individuals with a history of self-harm
- Selective Serotonin Reuptake Inhibitors (SSRI's)
 - Acutely increase the bioavailability of the neurotransmitter serotonin (5-HT) in the brain
- SSRI's first line of treatment for those with BPD and
 - Significant affective dysregulation
 - Co-morbid MDD

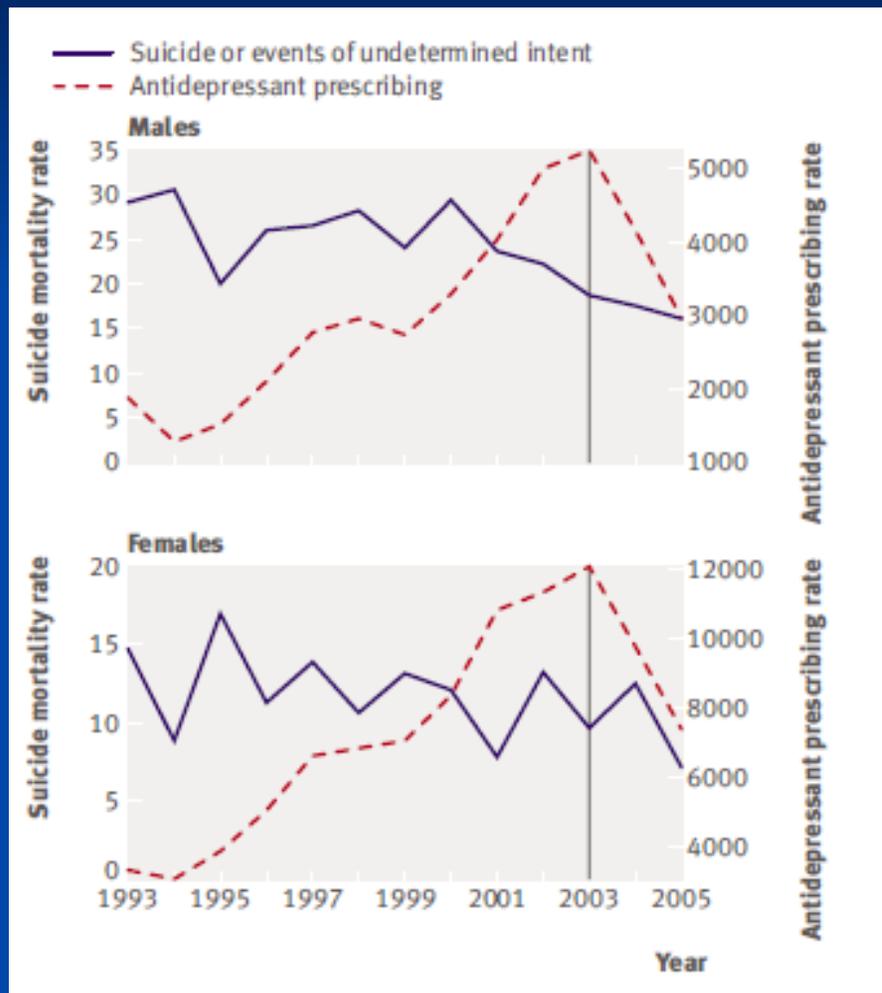
SSRIs and Suicidality: Overview

- SSRI's most commonly prescribed psychotropic medication
 - ~ 10% of individuals in US take SSRI's
- Early anecdotal and case study reports of increased self-harming behavior and ideation during the first month of treatment with SSRI's
- Meta-analysis of clinical trial data showed a modest increase in suicidality for pediatric patients.
- FDA black box warning on SSRIs,
 - Use could lead to suicidality among individuals under age 25.

SSRIs and Suicidality: Ecological Studies

- Ecological studies correlating SSRI use and national suicide rates do not support a link between SSRIs and suicide
 - Sweden, Hungary, Finland, Japan and England - inverse relationship between national rate of SSRI use and suicide.
 - Italy, Iceland, England – no relationship
 - Analysis of 27 European countries – inverse relationship
 - US - inverse relationship between child and adolescent antidepressant use and suicide
- However not causal relationship, does not address other self-harm ideation and behavior

SSRIs and Suicidality: Ecological Studies



Trends in adolescent (12-17) suicide rates and antidepressant prescribing in UK

Wheeler et al, 2007

SSRIs and Suicidality: Ecological Studies

Analysis of 27 European countries, Ludwig & Marcotte, 2005

Table 4. Regression estimates for international panel data by gender and age, years 1980 to 2000.

	Log Rate, Males	Log Rate, Females	Log Rate, Ages 10–14	Log Rate, Ages 15–24	Log Rate, Ages 25–34	Log Rate, Ages 35–44	Log Rate, Ages 45–54	Log Rate, Ages 55–64	Log Rate, Ages 65 +
SSRI doses sold per capita	-0.030** (.009)	-0.007 (.008)	-0.033 (.029)	-0.049** (.011)	-0.019 (.013)	-0.008 (.009)	0.002 (.009)	-0.019** (.009)	-0.017** (.008)
Model specification as in column 2 of Table 2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sample (N)	492	492	472	487	490	489	489	491	477
Adj. R-squared	0.987	0.982	0.967	0.967	0.969	0.980	0.980	0.980	0.988

Note: Table reports least squares regression coefficients, with standard errors in parentheses. Estimates calculated via weighted least squares using a model specified by equation (1), using country population as the weighting variable. A total of 27 country-year observations report no suicides to people in our youngest age group (10–14) during our study period. Since the natural logarithm of zero is undefined, our default is to set these rates equal to $\log(0.01)$, although we also experiment with setting these values equal to $\log(0.1)$, $\log(0.001)$, and to missing values. Sample consists of annual observations for 27 countries (see text). * = $p < .10$ ** = $p < .05$

SSRIs and Suicidality: Clinical Trials

- Retrospective (meta) analyses of clinical trials data are mixed, but stronger for younger patients
 - Large scale FDA meta-analysis (n = 48,277) found no difference in suicide rates between SSRIs, non-SSRI and placebo (ditto for Britain, Netherlands)
 - Analyses of SSRI risk for suicidal attempts/ideation have produced varying results
 - SSRIs decrease suicide attempt and ideation (e.g. Perlis et al, 2007)
 - SSRIs no effect on ... (e.g., Gibbons et al, 2007)
 - SSRIs increase suicidal ideation - meta-analyses of 24 pediatric RCT in the US (N = 4,582) and Europe (N = 3478).

SSRIs and Suicidality: Clinical Trials

TABLE 1. Suicide Rates Among Patients Participating in FDA Clinical Trials of Investigational Antidepressants

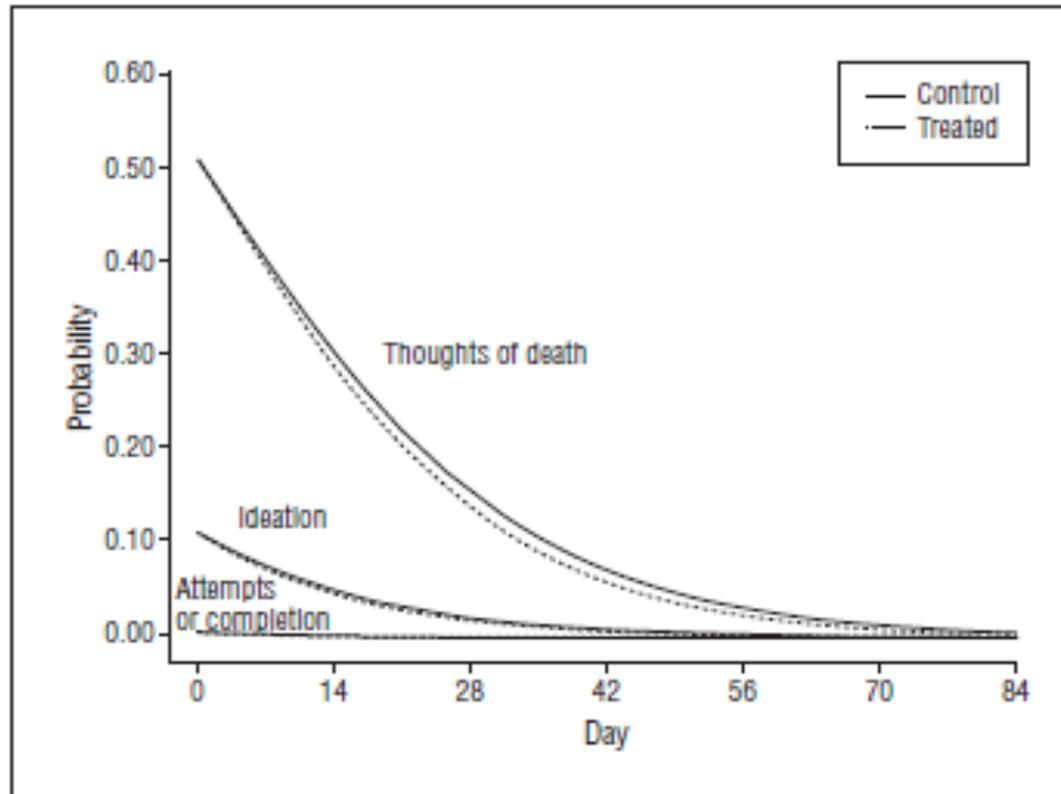
Treatment	Absolute Suicide Rate			Suicide Rate by Patient Exposure Years ^a				
	Number of Patients Randomly Assigned to Condition	Patient Suicides			Patient Exposure Years	Patient Suicides		
		N	%	95% CI		N	%	95% CI
Selective serotonin reuptake inhibitors ^b	26,109	38	0.15	0.10–0.20	2,864	17	0.59	0.31–0.87
Other antidepressants ^c	17,273	34	0.20	0.09–0.27	4,094	31	0.76	0.49–1.03
Placebo	4,895	5	0.10	0.01–0.19	897	4	0.45	0.01–0.89

^a Cumulative time that subjects were exposed to an investigational antidepressant, active comparator, or placebo while participating in a research program.

^b Sertraline, paroxetine, citalopram, fluoxetine, or fluvoxamine. Suicide rates based on patient exposure years were not available from the fluoxetine trials.

^c Nefazodone, mirtazapine, bupropion, maprotiline, trazodone, mianserin, dothiepin, imipramine, amitriptyline, or venlafaxine (either immediate or extended release). Suicide rates based on patient exposure years were not available from the bupropion trials.

SSRIs and Suicidality: Clinical Trials



Gibbon et al , 2012

SSRIs and NSSI

- The few studies conducted suggest a possible relationship between SSRIs and NSSI
 - Gunnell (2005) SSRIs were associated with an increased risk of self-harm (which included both suicide attempts and self-injurious behavior).
 - Similar results found in a sample of 57,000 patients taking antidepressants in New Zealand (Didham, 2005)

SSRIs and Self Harm

- Self-harm risk appears to be greatest during the first month of SSRI treatment
 - Early case studies showed suicidal ideation increase in 1st few weeks of treatment
 - Large case control study showed during 1st month of treatment SSRI increased risk of suicide (OR = 4.8) relative to other antidepressants
 - Meta-analysis results increased risk of suicidality within the first 1- 2 months of initiating treatment, with the greatest risk occurring during the first few weeks

SSRIs and Self Harm

- Individuals with more severe affect dysregulation deficits may be most vulnerable to possible paradoxical effect of SSRIs on self-harm
 - affect dysregulation (e.g. aggression, impulsivity, emotional lability), is associated with
 - Self-harming behavior
 - 5-HT dysregulation (which in turn is also associated with self-harming behavior)

Study

- Prospectively assess the impact of early SSRI treatment on self-harm among 200 subjects with BPD and depressive symptoms, aged 18-40.
- Independent Variable
 - Randomize participants to SSRI (escitalopram) or placebo for 8 weeks
 - Then all subject open label escitalopram for 8 weeks
- Dependent variables
 - Self-report of suicidal ideation, suicide attempts, NSSI, depressive symptoms, associated constructs
 - Behavioral Measure of self-harm

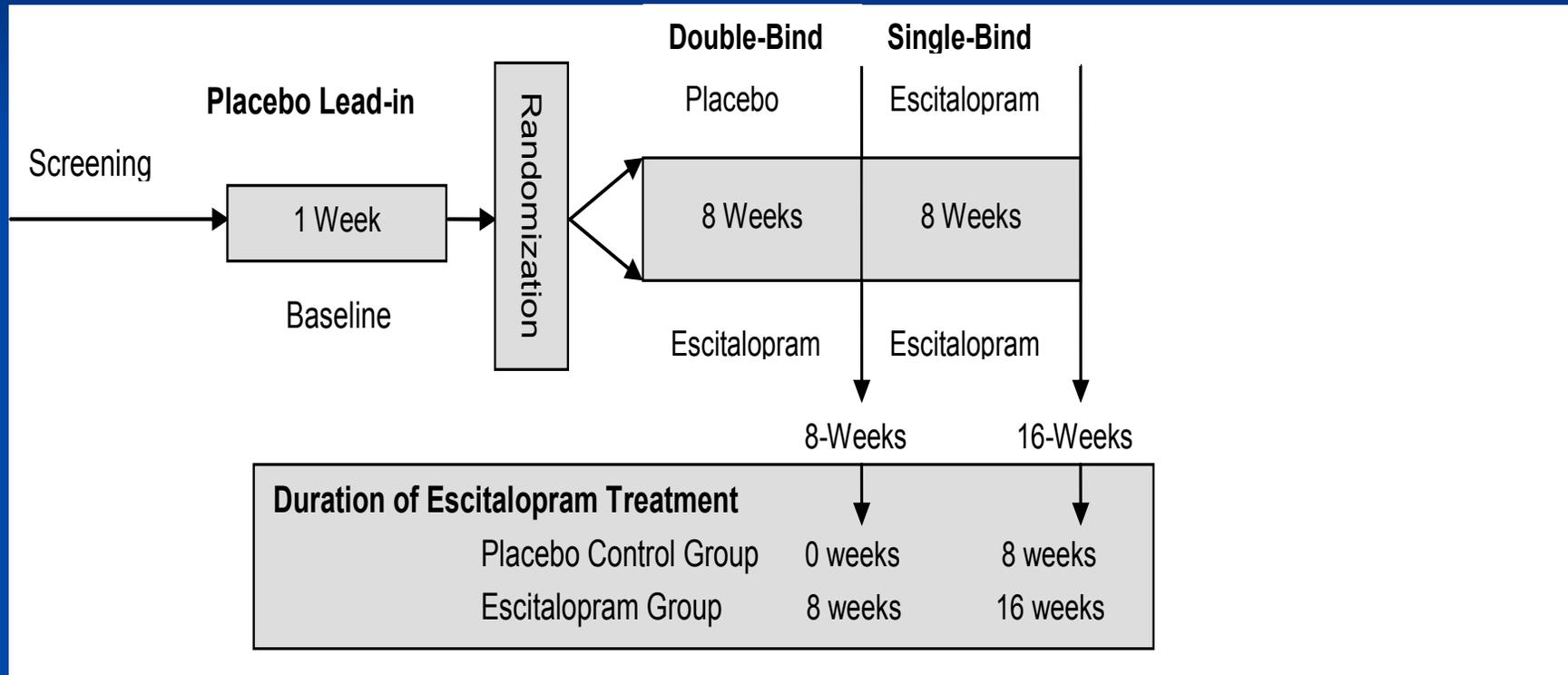
SSRIs and Self-harm in Borderline Personality Disorder

- Primary Hypotheses
 - Subjects randomized to the escitalopram condition will report less self-harm ideation and behavior compared to subjects in the placebo condition

SSRIs and Self-harm in Borderline Personality Disorder

- Secondary Hypotheses
 - Age will moderate the relationship between escitalopram and self-harm.
 - Affective dysregulation (e.g., impulsivity, aggression, poor socioemotional information processing) will moderate the relationship between escitalopram and self-harm.

Study Design



Participants

- 18-40 years old
- Meet for BPD
- Endorse significant depressive symptoms
- Not currently (past 6 months) using SSRIs or (2 months) other antidepressants

Measures

■ Self-harm

- Scale for Suicide Ideation-Self-Report (SSI)
- Suicide Attempt and Self-Injury Interview (SASII)
- Self-Aggression Paradigm (SAP)

■ Depression

- Hamilton Rating Scale for Depression (HAM-D)
- Beck Depression Inventory (BDI)
- Beck Hopelessness Scale (BHS)

Secondary Measures

- Emotion Regulation
 - Affect Lability Scale (ALS)
 - Difficulties in Emotion Regulation Scale (DERS)
 - Paced Auditory Serial Addition Task (PASAT)
 - Buss Perry Aggression Questionnaire (BPAQ)
 - UPPS Impulsivity Scale (UPPS)

Ecological Momentary Assessment

- 4 phone calls a day to assess
 - Suicidal and NSSI behavior and ideation
 - Depressive symptoms
 - Other momentary affect / Akathisia

Study to date

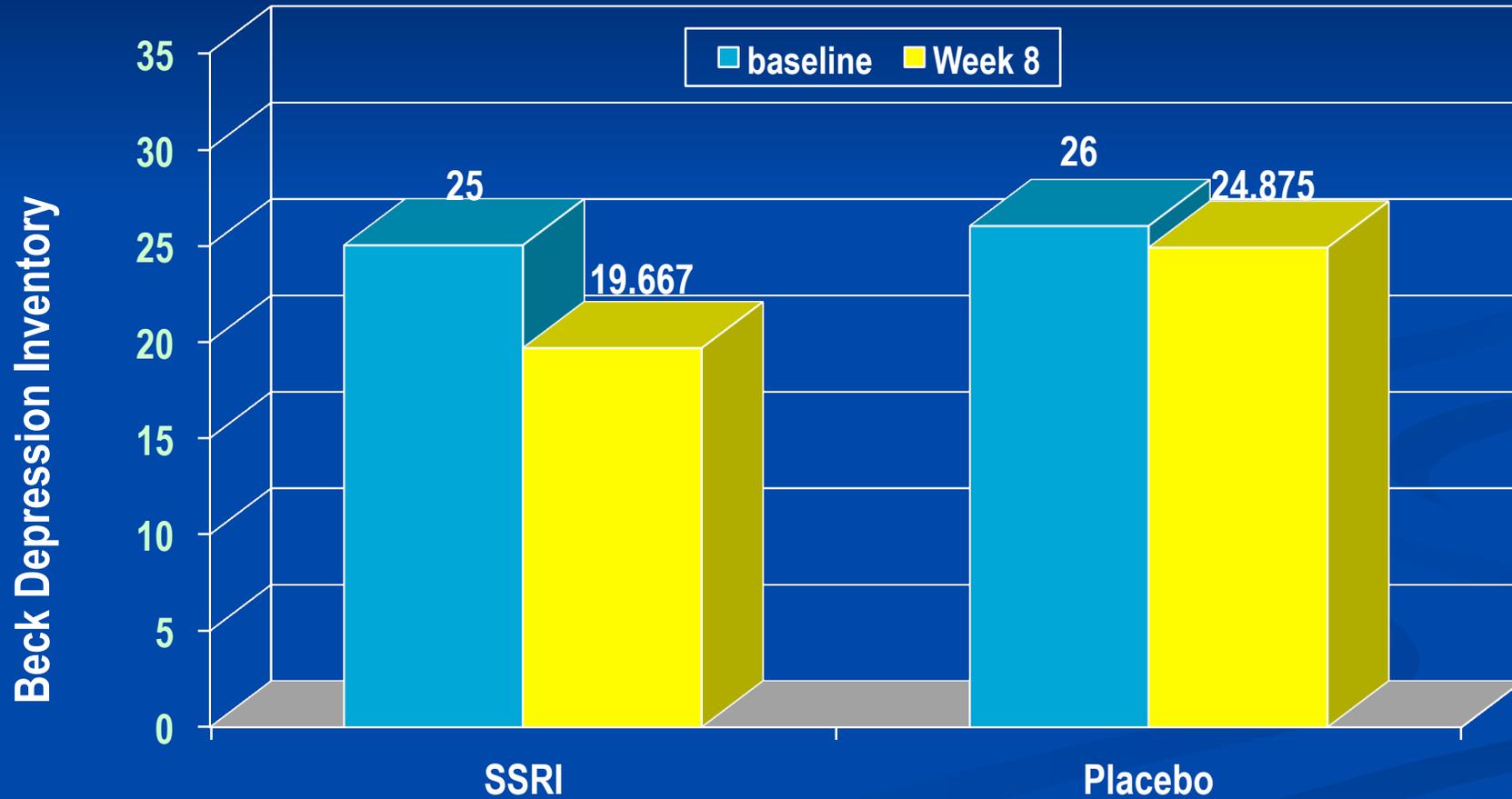
■ Participants

- 50 Completed baseline (27 placebo, 23 escitalopram)
- 25 Completed 8 week RCT (14 placebo, 11 escitalopram)

■ RCT completer characteristics*

- Age: $M = 29.78$ (11 participants < 25 years old)
- Gender: Female = 20, Male = 5
- Race : Caucasian = 11, AA = 10, Other = 4
- Past suicide attempts: $N = 9$ (past 2 months = 0)
- Past NSSI: $N = 14$ (past 2 months = 5)
 - No significant differences between participants in escitalopram and placebo condition on any demographic characteristics

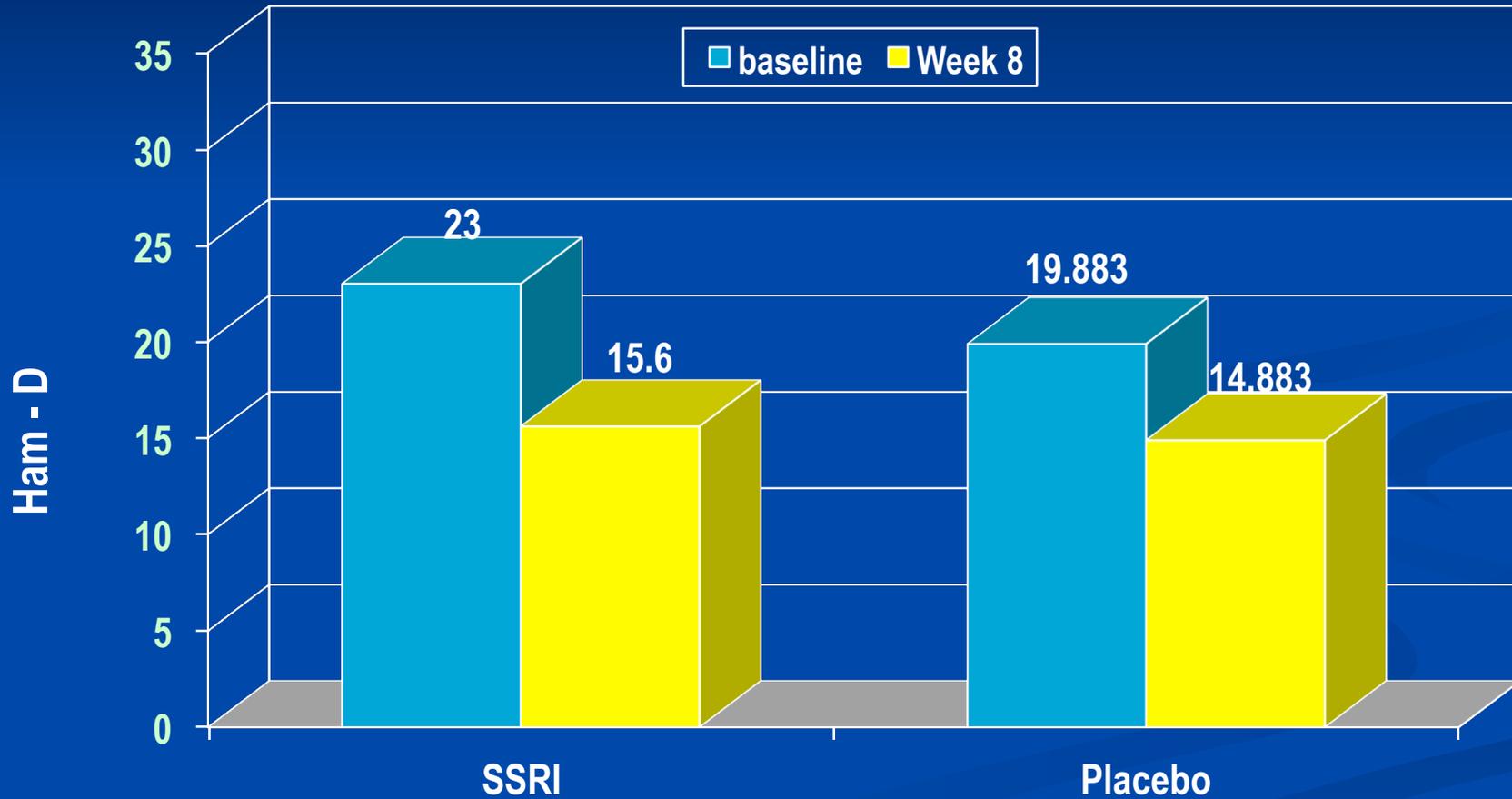
Effect of SSRI on Depressive Sx



* $p < .05$

$N = 25$, SSRI x time $p > .25$

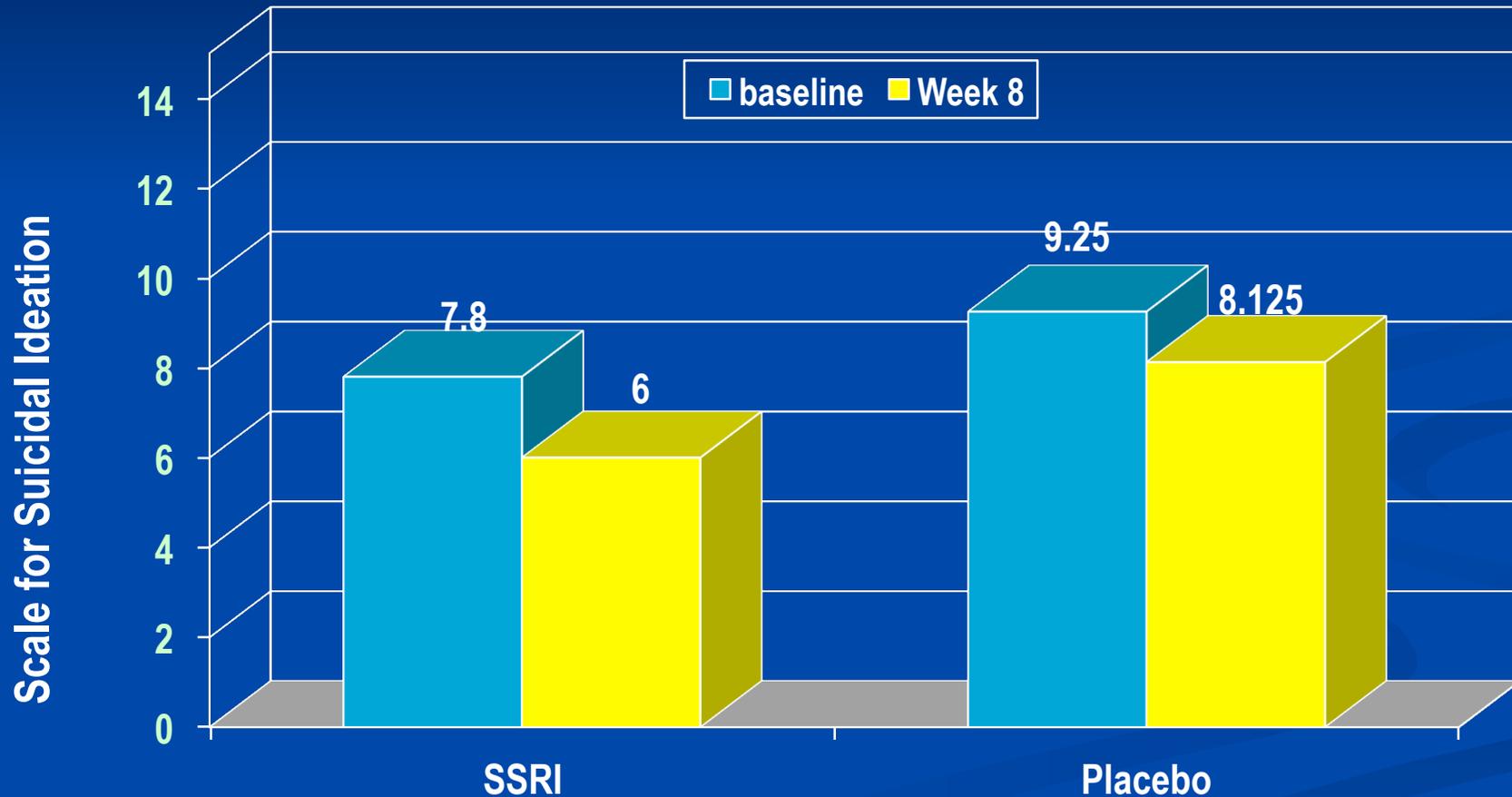
Effect of SSRI on Depressive Sx



* $p < .05$

N = 25, SSRI x time $p > .50$

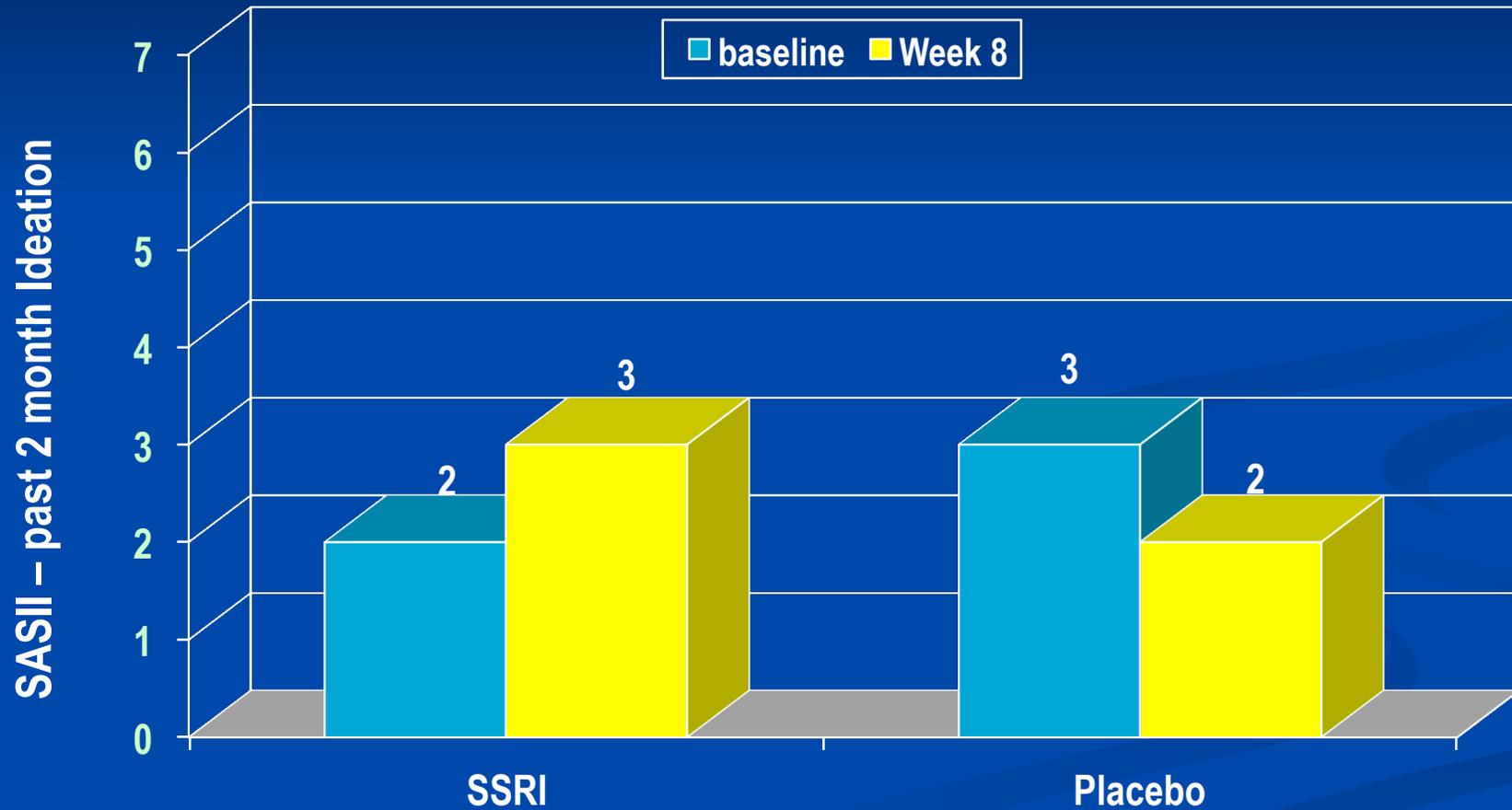
Effect of SSRI on Suicidal Ideation



* $p < .05$

N = 25, SSRI x time $p > .50$

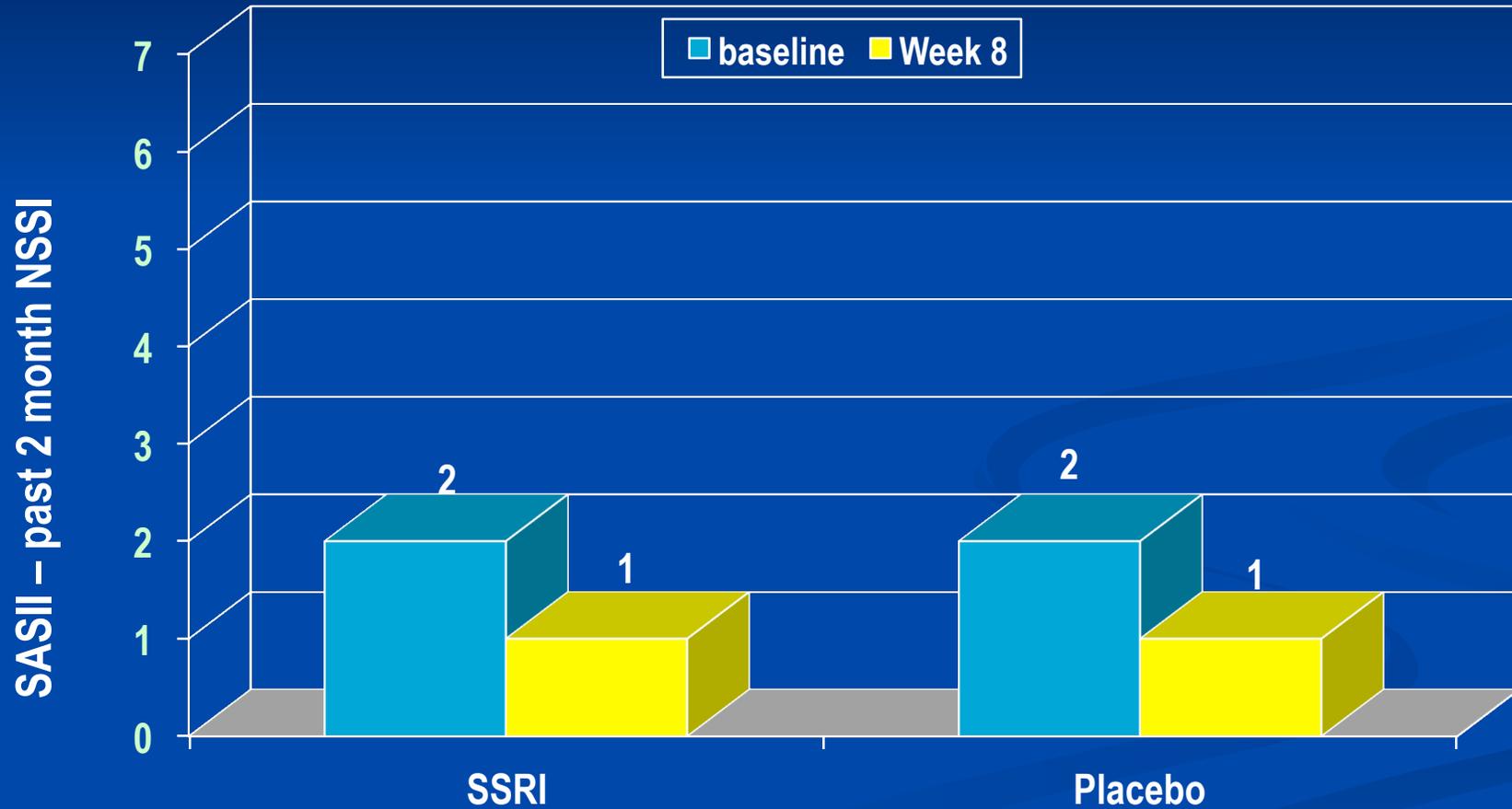
Effect of SSRI on NSSI Ideation



* $p < .05$

N = 22

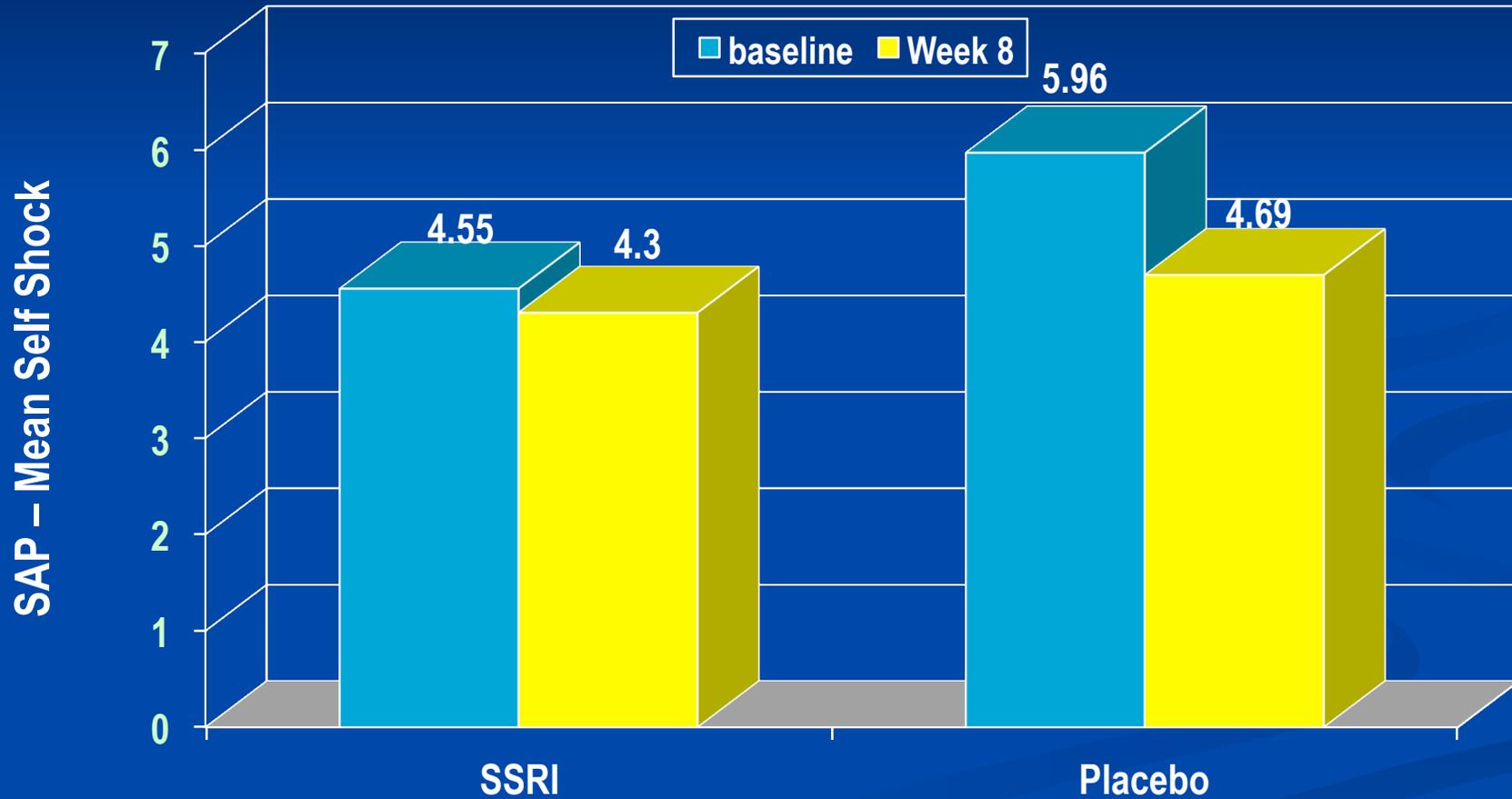
Effect of SSRI on NSSI



* $p < .05$

N = 22

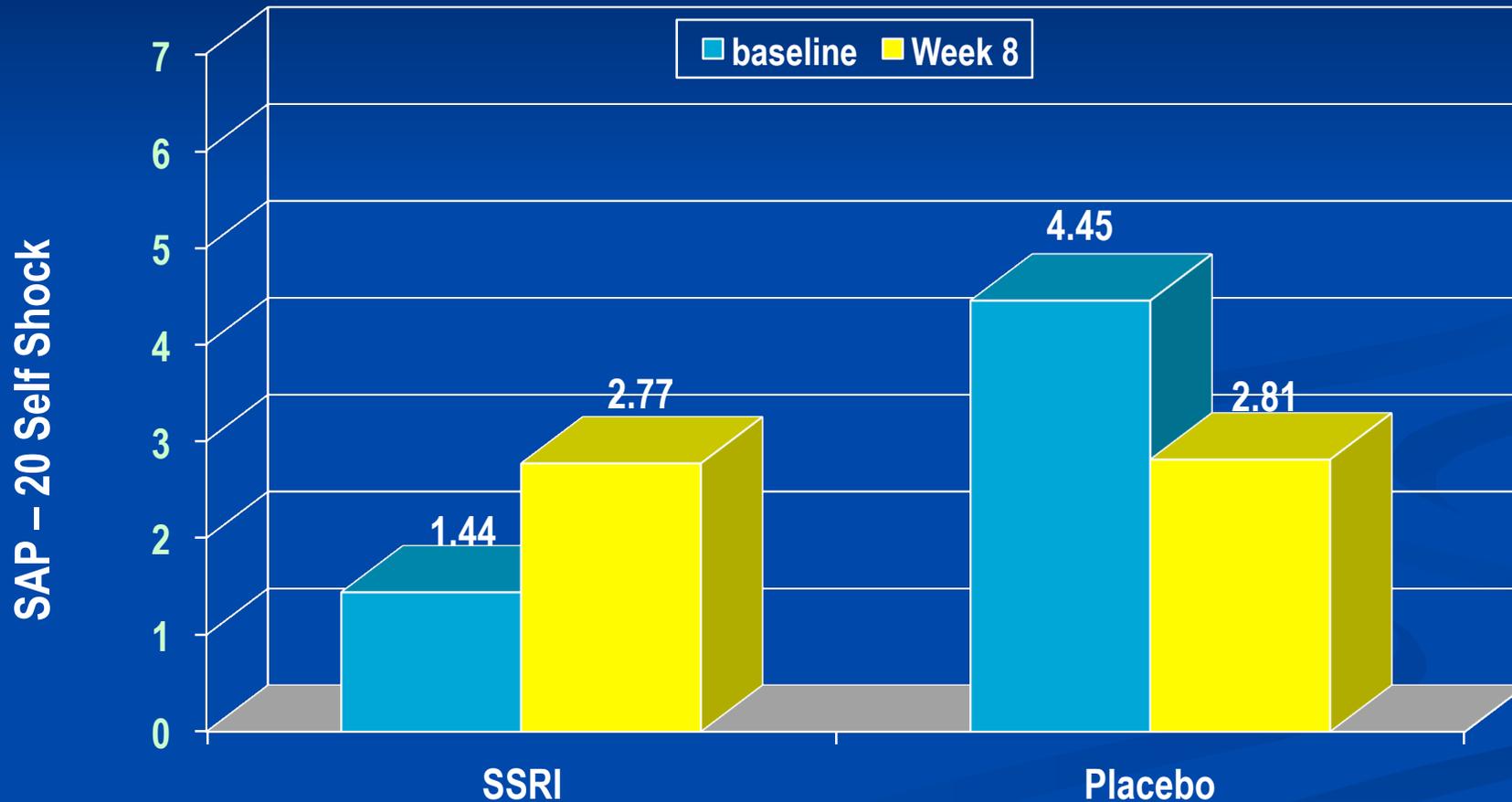
Effect of SSRI on Self-Aggression



* $p < .05$

N = 25, SSRI x time $p > .25$

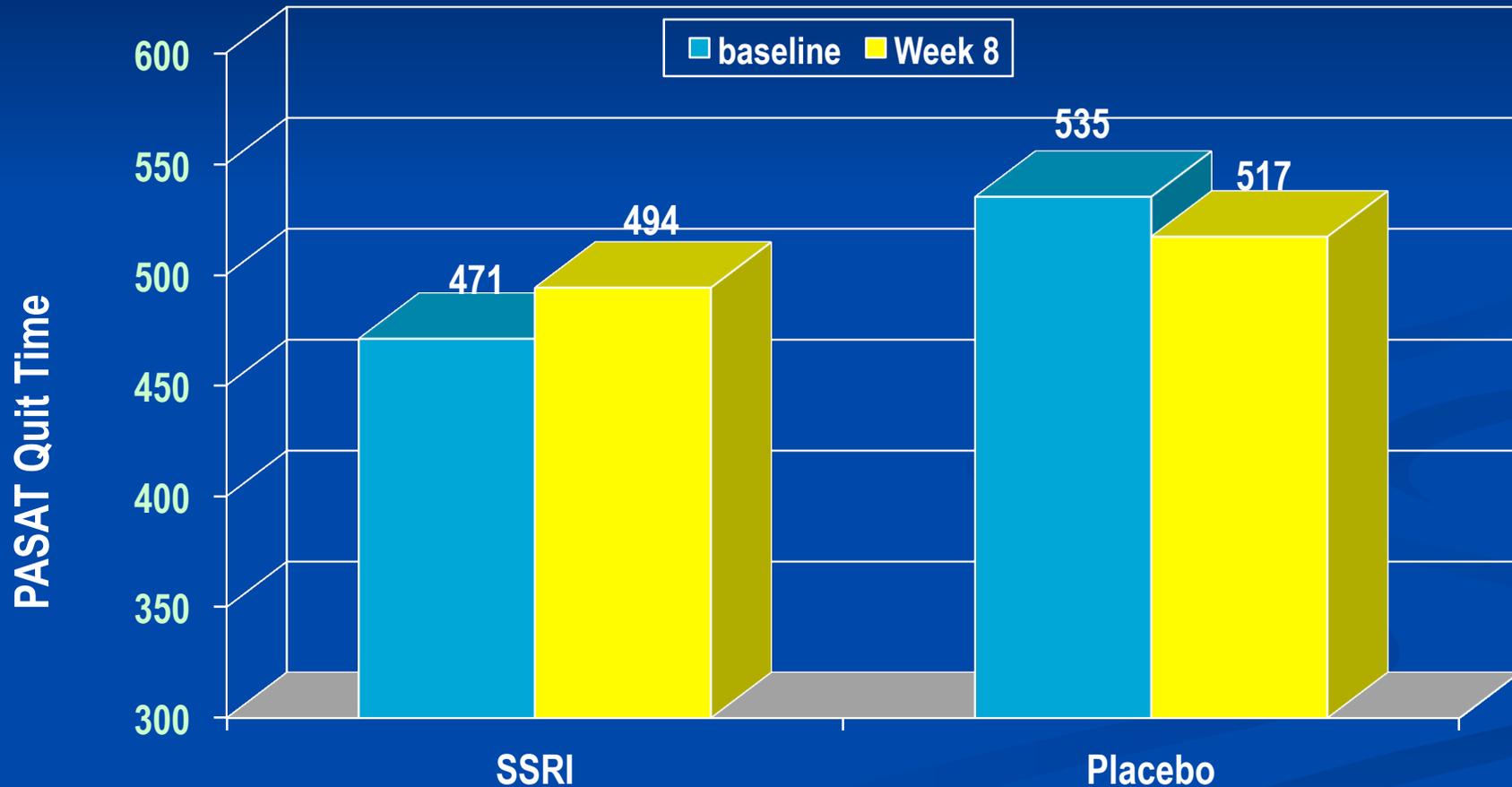
Effect of SSRI on Self-Aggression



* $p < .05$

N = 25, SSRI x time $p = .17$

Effect of SSRI on Distress Tolerance



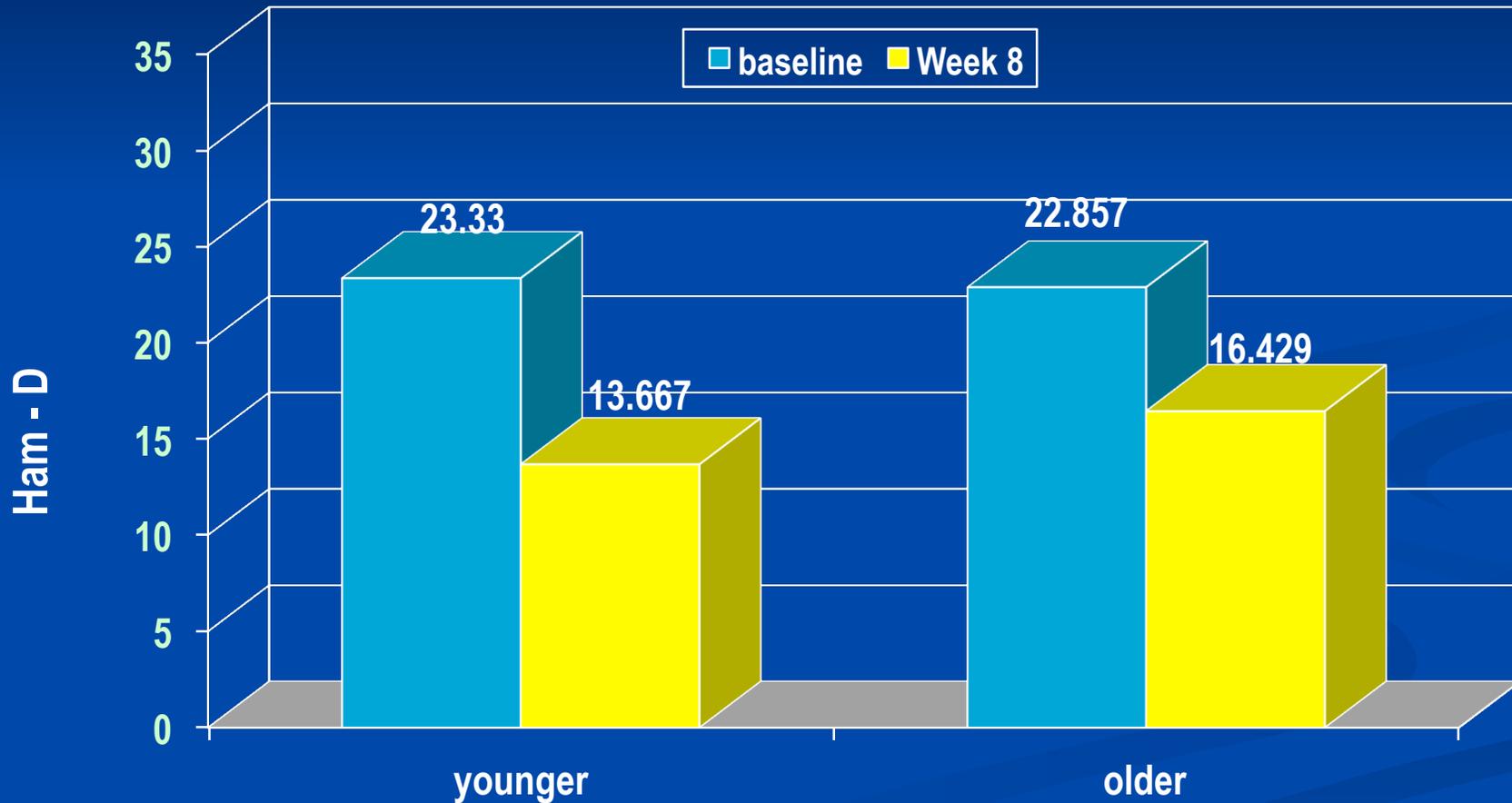
* $p < .05$

N = 25, SSRI x time $p = .17$

Escitalopram Participants 25 and under vs. 26 and over (Very Exploratory)

- 25 and under = 4
- 26+ = 7

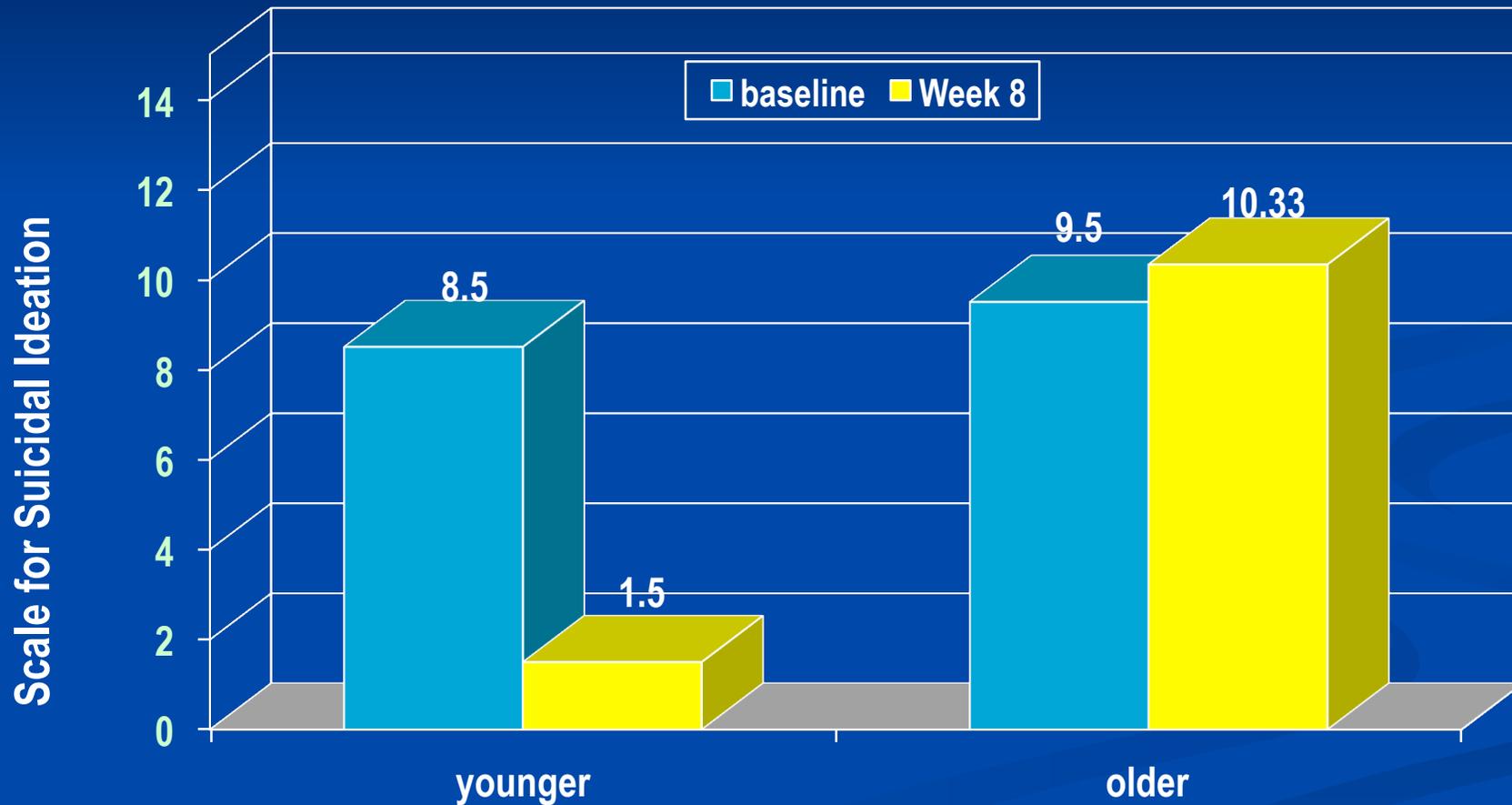
Effect of SSRI on Depressive Sx



* $p < .05$

N = 11

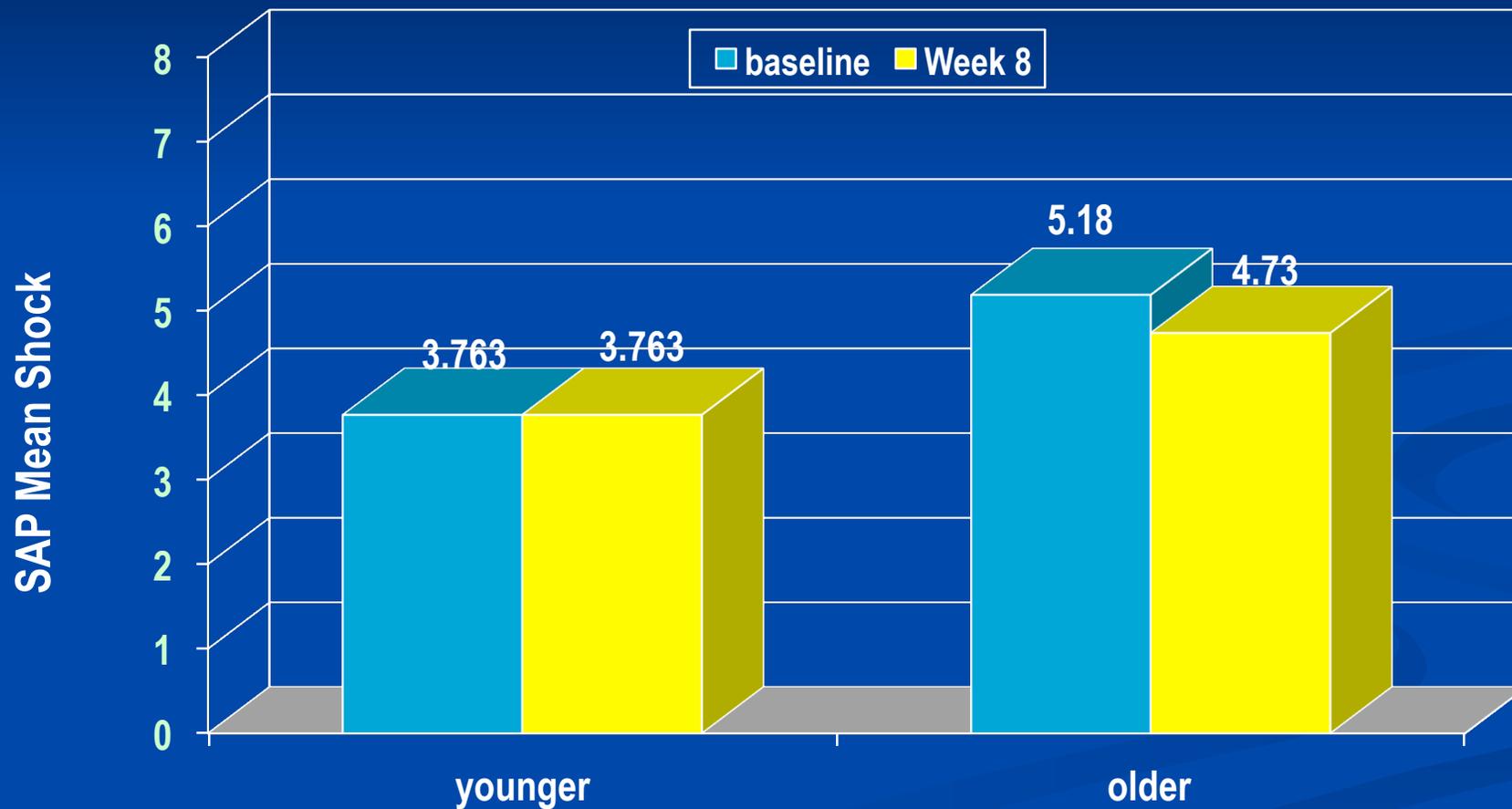
Effect of SSRI on Suicidal Ideation



* $p < .05$

N = 11

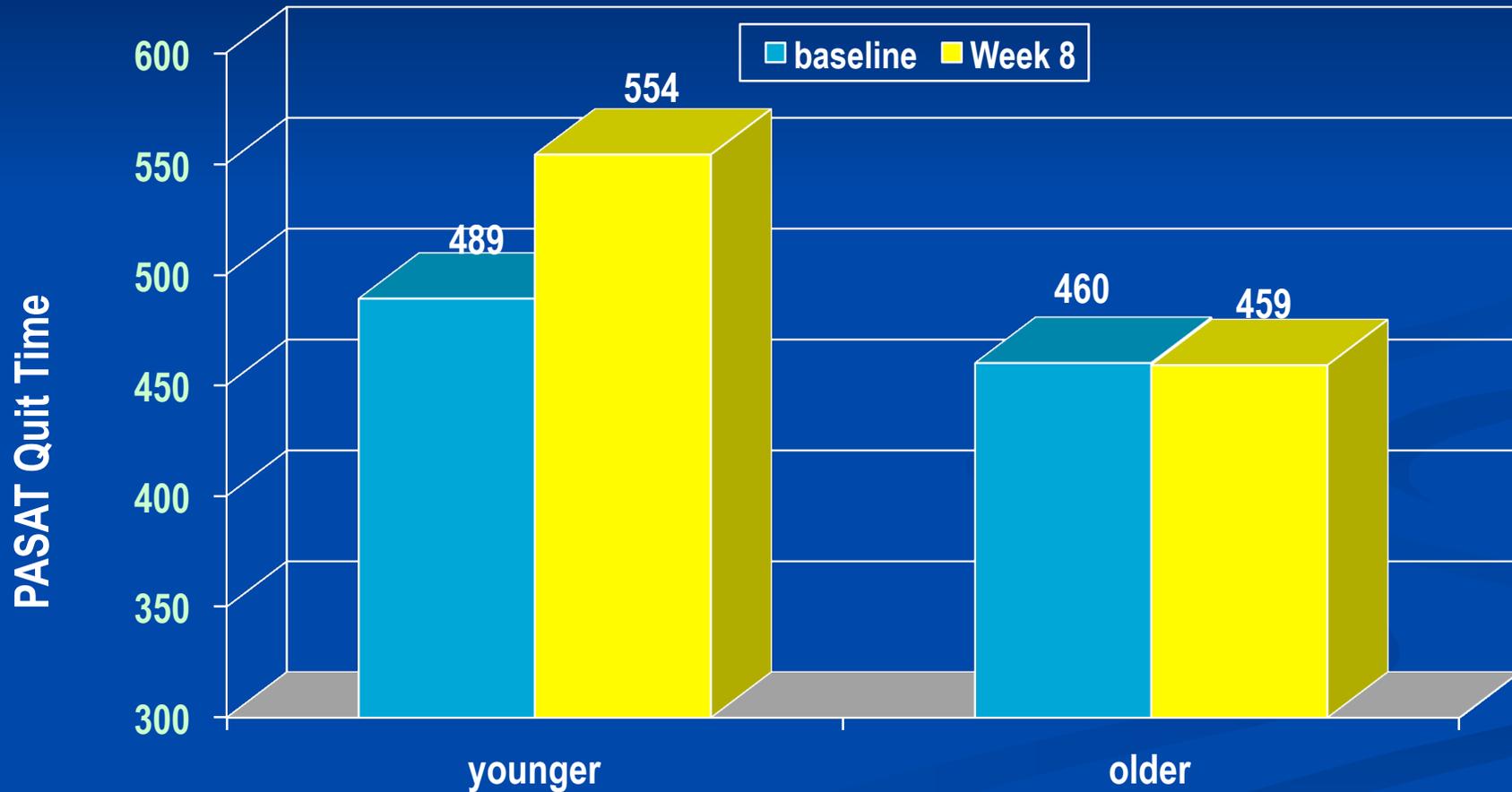
Effect of SSRI on Self-Harm



* $p < .05$

N = 11

Effect of SSRI on Distress Tolerance



* $p < .05$

N = 11

Summary

- Research is mixed on the effects of SSRIs on self-harming behavior and ideation
- If SSRI's do potentiate self harm , it is most likely to occur early in treatment and among individuals who are (a) younger and / or (b) have greater affective dysregulation
- To examine this a prospective short duration RCT is comparing SSRI to placebo for individuals with BPD and depressive symptoms
- Early findings using self-report and behavioural measures are mixed. A larger sample and the analysis of more nuanced measures (e.g., EMA) will be needed to better address the question.

Collaborators

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