

# Is suicidal depression a specific phenotype ? (... More than depression?)

**Philippe Courtet**

# Disclosure of conflict of interest

- **Fondamental Foundation**
- **Exeltis**
- **Janssen**
- **Servier**
- **Otsuka**

# Unmet needs

- In depression, the population attributable risk of mood disorders for a first occurrence of SI or SA has been estimated at 51% - 44%
- Thus, reducing the duration of depressive episodes might have a major impact on suicidal risk
- American Psychiatric Association practice guideline on management of patients with suicidal behaviour: “*Evidence for a lowering of suicide rates with antidepressant treatment is inconclusive*”
- Total absence of treatments for acutely suicidal patients

Practice guide for the assessment and treatment of patients with suicidal behaviors. Available at [https://psychiatryonline.org/pb/assets/raw/sitewide/practice\\_guidelines/guidelines/suicide.pdf](https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/suicide.pdf). Accessed August 2018

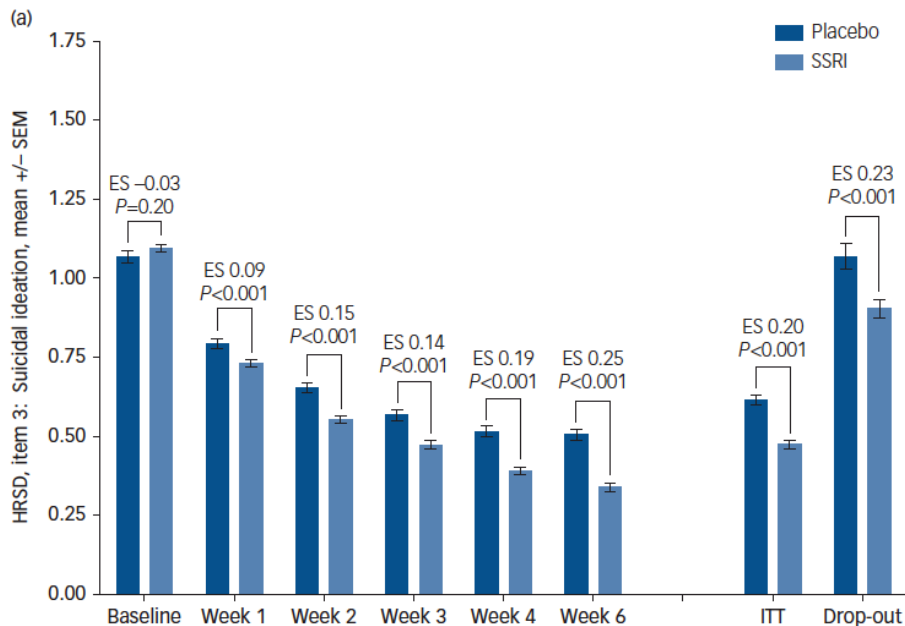
Nock et al 2010

Sokero et al 2003

# Effects of selective serotonin reuptake inhibitors on rating-scale-assessed suicidality in adults with depression

The British Journal of Psychiatry (2018)

Jakob Näslund, Fredrik Hieronymus, Alexander Lisinski, Staffan Nilsson and Elias Eriksson



**SSRI (n = 5681)**  
**placebo (n = 2581)**

**HDRS-SI $\geq$ 3 : < 6%**

HRSD-17	0	Absent
	1	Feels life is not worth living
	2	Wishes he/she were dead, or any thought of possible death to self
	3	Suicide ideas or half-hearted attempt
	4	Attempts suicide

# **Suicidal depression**

- 1. Two cohort studies : Short term follow-up**
- 2. Clinical sample of depressed patients : 2 years follow-up**

# Two cohorts of unipolar depressed outpatients, 6 weeks follow-up

initiation of antidepressant  
treatment



Cohort 1

Cohort 2

Self reports :

Suicidal Ideation : *MADRS suicide item*

Depression, anxiety : *Hospital Anxiety and Depression Scale*

*Beck Hopelessness Scale*

Sleep (*MADRS sleep item*)

Impulsivity (*Plutchik Impulsivity Scale*)

MADRS	0 to 1	Enjoys life or take it as it comes
	2 to 3	Weary of life. Only fleeting suicidal thoughts.
	4 to 5	Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intentions.
	6	Explicit plans for suicide when there is an opportunity. Active preparation of suicide

	Total population		HADS-D $\geq 11$ (MADRS $\geq 20$ )		Non suicidal depression (MADRS-SI $< 2$ )		Moderately suicidal depression (MADRS-SI [2; 4[)		Severely suicidal depression (MADRS-SI $\geq 4$ )	
	N	%	N	%	N	%	N	%	N	%
<b>Cohort 1</b>	<b>4845</b>		<b>3969</b>	<b>81,9</b>	<b>671</b>	<b>16,9</b>	<b>2292</b>	<b>57,7</b>	<b>1006</b>	<b>25,3</b>
<b>Cohort 2</b>	<b>3566</b>		<b>2537</b>	<b>71,1</b>	<b>370</b>	<b>14,6</b>	<b>1408</b>	<b>55,5</b>	<b>759</b>	<b>29,9</b>

# Baseline sociodemographic characteristics

Variable	Suicidal Depression (COHORT 1)								Suicidal Depression (COHORT 2)							
	No		Moderate		Severe		Global p-value	Adj. p-value	No		Moderate		Severe		Global & adj. p-value	
	n	% (SD)	n	% (SD)	n	% (SD)			n	% (SD)	n	% (SD)	n	% (SD)		
Gender Women	425	63.3	1456	63.5	644	64.0	0.95	0.98	226	61.1	844	59.9	480	63.2	0.32	0.41
Age (years)	47.51 (14.32)		47.37 (13.70)		47.65 (14.04)		0.86	0.87	48.02 (14.64)		49.30 (14.58)		50.61 (14.82)		0.02	0.009
Marital Status Married	415	62.3	1246	54.6	508	50.6	0.006	0.002	236	64.0	817	58.2	405	53.5	0.02	0.003
Children	513	77.1	1719	75.7	750	75.1	0.62	0.69								
Living alone	191	28.9	812	35.8	391	39.5	<0.001	0.003								
Study level Under bachelor	273	41.0	910	40.1	456	45.7	0.06	0.12	147	40.4	607	43.3	378	50.2	0.002	0.34
Professional activity Working	364	57.5	1237	56.8	482	50.2	0.02	0.16	223	61.1	764	54.6	352	46.9	<0.001	0.01

Global p-value adjusted on depression severity for COHORT 1 and on depression severity and age for COHORT 2



# Baseline clinical characteristics

Variable	Suicidal Depression (COHORT 1)							Suicidal Depression (COHORT 2)								
	No		Moderate		Severe		Global p-value	Adj. p-value	No		Moderate		Severe		Global & adj. p-value	
	n	% (SD)	n	% (SD)	n	% (SD)			n	% (SD)	n	% (SD)	n	% (SD)		
Current MDE duration (≥ 6 months)	25	3.8	73	3.2	38	3.8	0.79	0.80	75	20.6	313	22.7	224	30.1	<0.001	0.001
Number of MDE lifetime	1.58 (7.87)		1.48 (5.85)		2.42 (9.06)		0.005	0.03	2.22 (1.31)		2.74 (2.98)		3.19 (2.85)		<0.001	<0.001
Age at first MDE (years)	36.21 (13.11)		34.73 (12.16)		33.60 (12.49)		0.009	0.03	36.68 (14.72)		36.54 (13.77)		35.54 (13.67)		0.50	0.70
HAD-A Baseline	13.46 (3.41)		14.55 (3.22)		16.07 (3.23)		<0.001	<0.001	13.52 (3.32)		14.14 (3.24)		15.46 (3.45)		<0.001	<0.001
HAD-D Baseline	15.04 (2.37)		15.99 (2.66)		17.79 (2.55)		<0.001	NA	14.76 (2.38)		15.34 (2.46)		16.70 (2.72)		<0.001	<0.001
HAD total score Baseline	28.50 (4.51)		30.54 (4.71)		33.85 (4.67)		<0.001	NA	28.28 (4.62)		29.47 (4.54)		32.16 (4.99)		<0.001	<0.001
Treatment Change (vs. new one)	108	16.5	427	19.1	297	30.6	<0.001	<0.001	57	15.5	247	17.7	186	24.8	<0.001	<0.001

Global p-value adjusted on depression severity for COHORT 1 and on depression severity and age for COHORT 2

# Baseline psychopathology

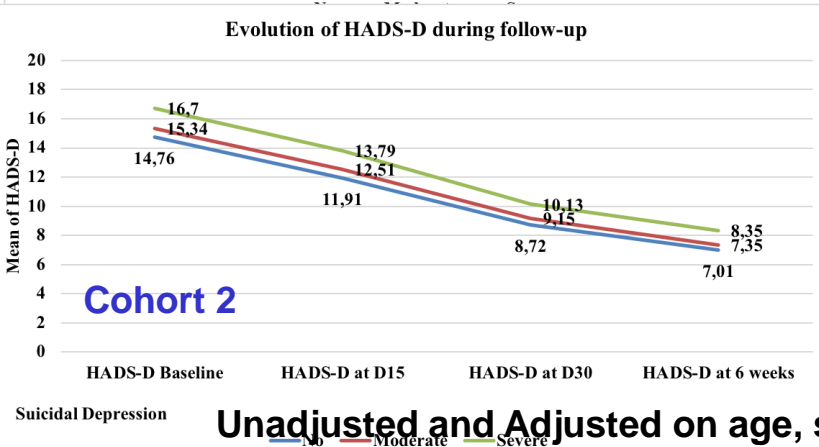
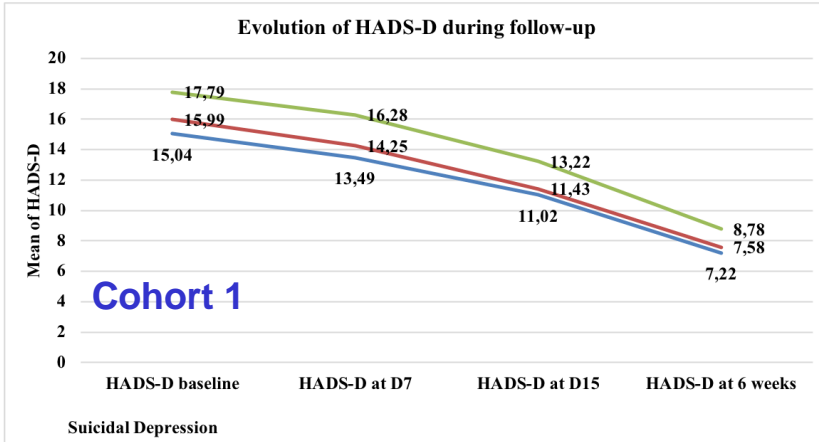
Variable	Suicidal Depression (COHORT 1)							Suicidal Depression (COHORT 2)							
	No		Moderate		Severe		Global p-value	Adj. p-value	No		Moderate		Severe		Global & adj. p-value
	n	% (SD)	n	% (SD)	n	% (SD)			n	% (SD)	n	% (SD)	n	% (SD)	
Hopelessness scale score Baseline	10.76 (2.13)		11.22 (1.82)		11.42 (1.39)		<0.001	<0.001							
Impulsivity scale score Baseline									36.08 (5.73)		36.93 (6.11)		38.42 (6.72)		<0.001 <0.001
MADRS-Sleep Baseline									3.12 (1.58)		3.65 (1.34)		4.26 (1.42)		<0.001 <0.001
Lifetime suicide attempts	36	5.4	387	17.0	373	37.1	<0.001	<0.001	17	4.7	119	8.7	177	23.9	<0.001 <0.001
Alcohol dependence	36	5.4	133	5.8	74	7.4	0.16	0.46							
Treatment associated	69	10.3	343	15.1	262	27.0	<0.001	<0.001	194	52.4	610	43.3	269	35.4	<0.001 <0.001

Global p-value adjusted on depression severity for COHORT 1 and on depression severity and age for COHORT 2

# Suicide attempt during 6 weeks follow up

	<i>No SA during follow-up</i>	<i>SA during follow-up</i>	OR [95% CI]	p-value	OR [95% CI]	Adjusted p-value (lifetime SA)
<i>COHORT 1</i>	N= 3567	N= 68				
No SI	601 (16.8)	2 (2.9)	-	<0.001	-	<0.001
Moderate SI	2063 (57.8)	24 (35.3)	3.50 [0.82; 14.83]		2.62 [0.61; 11.20]	
Severe SI	903 (25.3)	42 (61.8)	13.98 [3.37; 57.96]		8.08 [1.90; 34.26]	
<i>COHORT 2</i>	N= 2462	N= 15				
No SI	359 (14.6)	0				
Moderate SI	1367 (55.8)	8 (53.3)				
Severe SI	726 (29.6)	7 (46.7)				

# Evolution of severity of depression



- At each time point: higher depression scores in Severe SI
- Improvement of depression in each group
- Non difference in improvement of depression between groups

Unadjusted and Adjusted on age, study level, SA lifetime, MDE duration, treatment associated

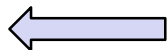
# Remission of depression (HAD-D $\leq 7$ ) at 6 weeks

Variables	Remission of Depression				Model 0		Model 1	
	No		Yes		OR [IC à 95%]	p-value	OR [IC à 95%]	p-value
	n	%	n	%				
<b>Suicidal depression</b>								
<b>COHORT 1</b>								
No	289	15.1	333	18.8		<0.001		0.001
Moderate	1054	55.1	1060	60.0	0.87 [0.73; 1.04]		0.92 [0.76; 1.11]	
Severe	570	29.8	375	21.2	0.57 [0.47; 0.70]		0.68 [0.54; 0.86]	
<b>Suicidal depression</b>								
<b>COHORT 2</b>								
No	166	13.2	191	15.8		<0.001		0.02
Moderate	676	53.7	705	58.5	0.91 [0.72; 1.14]		0.92 [0.72; 1.17]	
Severe	418	33.2	310	25.7	0.65 [0.50; 0.83]		0.71 [0.54; 0.94]	

Model 0: Crude association  
 Model 1: Adjusted on age, marital status, study level, actual MDE duration, lifetime SA, HADS total score baseline and associated treatment

## Remission rates

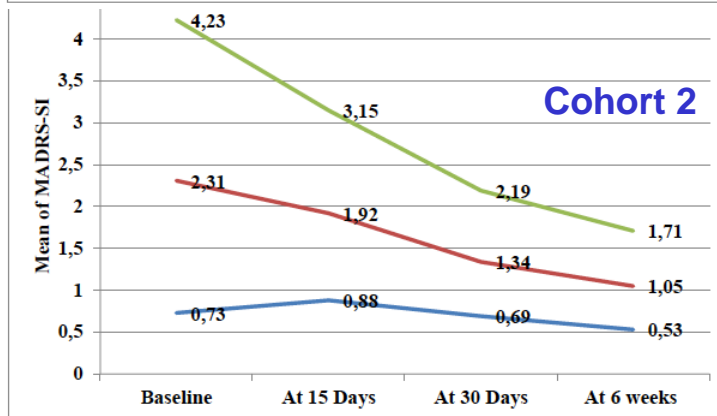
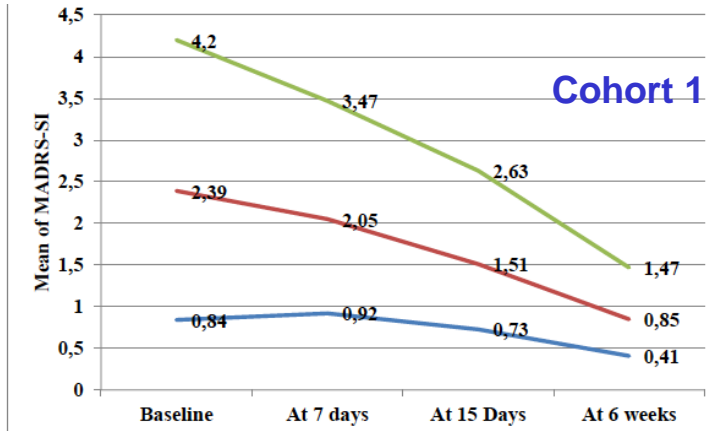
53.5%  
 50.1%  
 39.7%



53.5%  
 51.0%  
 42.6%



# Evolution of MADRS-SI in the 3 groups



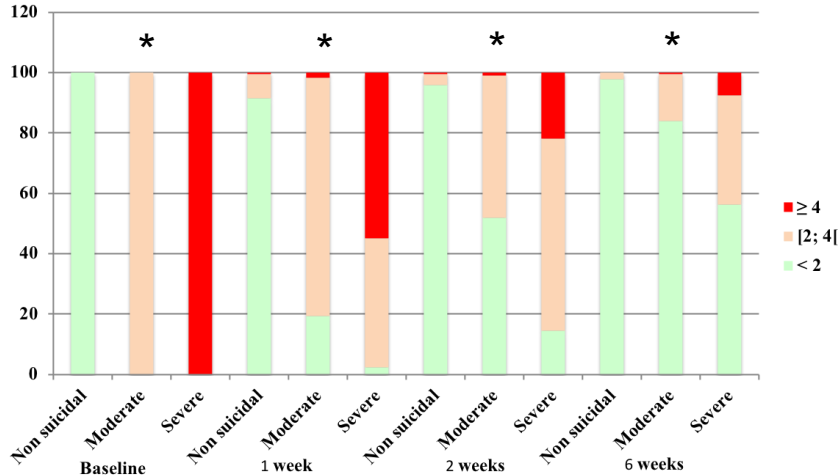
- At each time point: higher MADRS-SI scores in Severe SI
- Improvement of MADRS-SI scores in each group
- Better Improvement of MADRS-SI in Severe SI

**Unadjusted and Adjusted on age, study level, SA lifetime, MDE duration, treatment associated & on Depression at baseline or at each time or to the previous evaluation**

# Evolution of prevalence of SI in the 3 groups

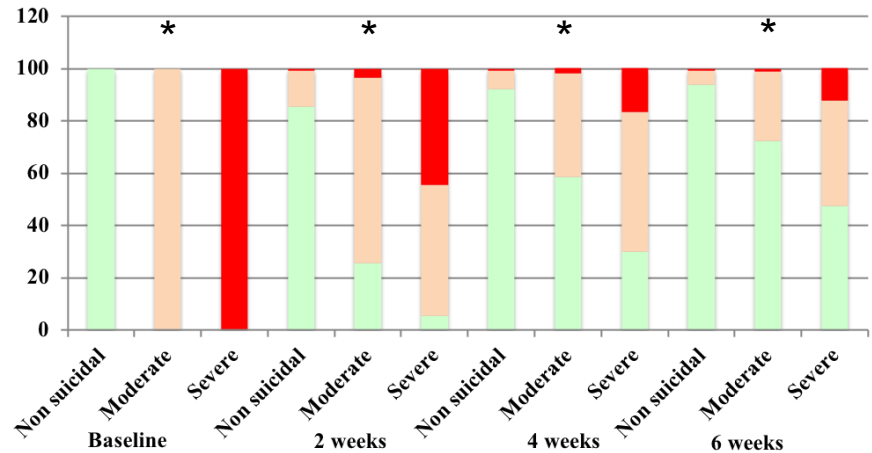
54.9%    21.9%    7.4%

Evolution of MADRS-SI during follow-up (COHORT 1)



44.3%    16.7%    12.2%

Evolution of MADRS-SI during follow-up (COHORT 2)



**Unadjusted and Adjusted on age, study level, SA lifetime, MDE duration, treatment associated & on Depression at baseline or at each time or to the previous evaluation**

# Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study

*Am J Psychiatry 175:7, July 2018*

Carla M. Canuso, M.D., Jaskaran B. Singh, M.D., Maggie Fedgchin, Pharm.D., Larry Alphas, M.D., Ph.D., Rosanne Lane, M.A.S., Pilar Lim, Ph.D., Christine Pinter, M.S., David Hough, M.D., Gerard Sanacora, M.D., Ph.D., Hussein Manji, M.D., Wayne C. Drevets, M.D.

## Suicidal Remissions (MADRS-SI=0-1)

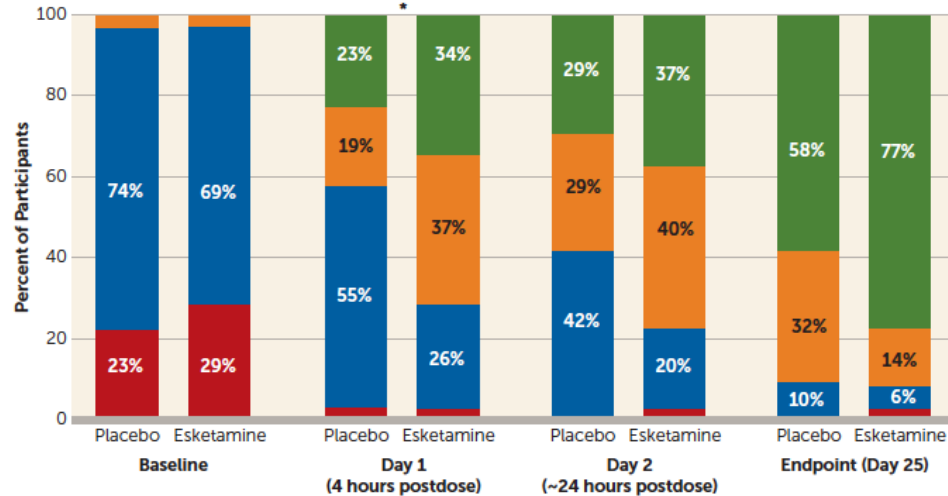
Our results : W4 30%

Canuso: W4 58% pcb (77% esket)

## Severe SI (MADRS-SI≥4)

Our results : W4 17%

Canuso: 10% pcb (7% esket)





**A persisting severe suicidal ideation  
is associated with the risk of suicide attempt  
during follow up:  
OR: 4.38 [2.05; 9.35]**

# Predictors of persistence of severe SI

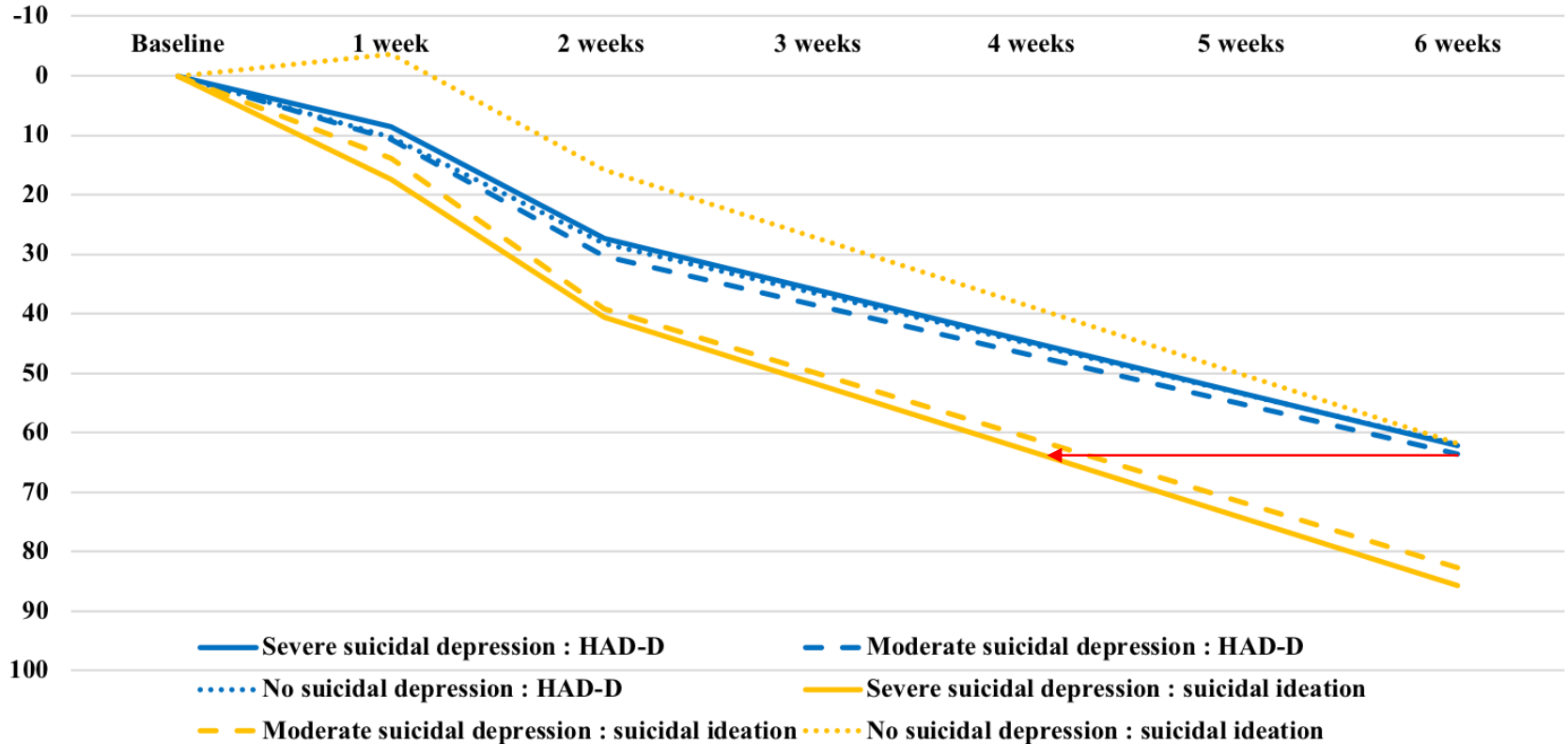
	COHORT 1		COHORT 2	
	<i>OR [95%CI]</i>	<i>p-value</i>	<i>OR [95%CI]</i>	<i>p-value</i>
<i>Variable</i>				
Study level		-		-
Current MDE duration ( $\geq 6$ months)	0.58 [0.06; 5.53]	-	1.69 [0.79; 3.61]	-
Number of MDE lifetime	1.02 [0.94; 1.10]	-		
Age at first MDE (years)	1.02 [0.98; 1.06]	-		
MADRS-SI Baseline	6.72 [4.43; 10.18]	<0.001	2.69 [2.08; 3.49]	<0.001
Lack of Change in HAD total	1.52 [1.35; 1.70]	<0.001	1.16 [1.10; 1.21]	<0.001
Lack of Change in Hopelessness	1.10 [0.91; 1.32]	-		
Lack of Change in impulsivity			1.01 [0.95; 1.08]	
Lack of Change in MADRS-sleep			1.38 [1.12; 1.69]	0.003
Lifetime SA	1.84 [0.68; 5.01]	-	1.28 [0.68; 2.41]	-
Treatment change	3.00 [1.11; 8.09]	0.03	0.92 [0.50; 1.70]	

# Summary

- **In 2 large independent cohorts of depressed unipolar outpatients, suicidal depression is :**
- **More severe at baseline (risk factors, depressive illness, anxiety, depression, hopelessness, impulsivity, sleep, history of suicide attempts)**
- **During the 6 weeks follow up:**
  - **Higher risk of suicide attempts**
  - **Suicidal ideation still more severe (controlling for depression)**
  - **Less remission of depression**

# Percentage symptom reduction from baseline for depressive symptoms and suicidal ideation

Percentage of diverse symptoms reduction (COHORT 1)



# Suicidal depression may be a subtype of MDD

- **Distinct psychiatric comorbidities and clinical and sociodemographic features**
  - **Age at onset of depression and childhood abuse**
  - **More frequent history of suicide attempt**
- **A propensity to severe suicidal ideation**
- **An actual risk of suicide attempts in short and long terms**
- **Response to antidepressant  $\pm$**

# Acknowledgements

**Dr E Olié**

**Dr B Nobile**

**Mr A Alacreu**