Il paziente depresso con anedonia: sintomi, trattamento e strategie di switch.

Il punto di vista dello psichiatra.

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Introduction: Andrea Fagiolini

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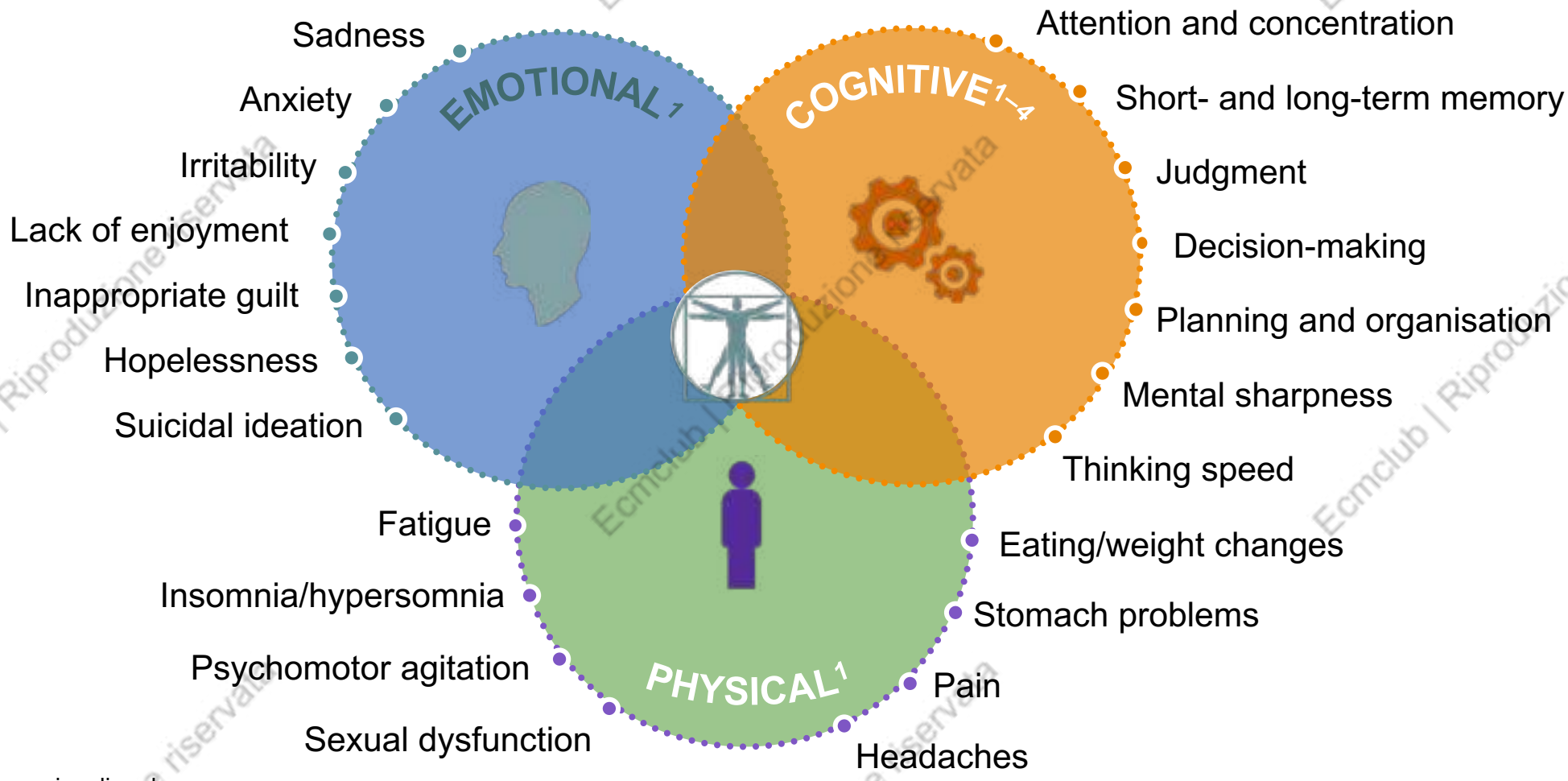
I have an interest in relation to one or more organisations that could be perceived as a possible conflict of interest in the context of the subject of this presentation.
The relationships are summarised below

DISCLOSURES	
Advisory board or similar committee	Angelini; Aspen; Boehringer Ingelheim; Janssen; Lundbeck; Otsuka; Recordati; Sanofi Aventis
Clinical trials or studies	Allergan; Angelini; Janssen; Lundbeck; Mylan; Otsuka
Honoraria or other fees	Allergan; Angelini; Aspen; Boehringer Ingelheim; Daiichi Sankyo Brasil Farmacêutica; DOC Generici; FB Health; Italfarmaco; Janssen; Lundbeck; Mylan; Otsuka; Pfizer; Recordati; Sanofi Aventis; Sunovion; Vifor
Research grants	Allergan; Angelini; Italfarmaco; Janssen; Lundbeck; Mylan; Otsuka

Symptom domains of MDD[1-4]

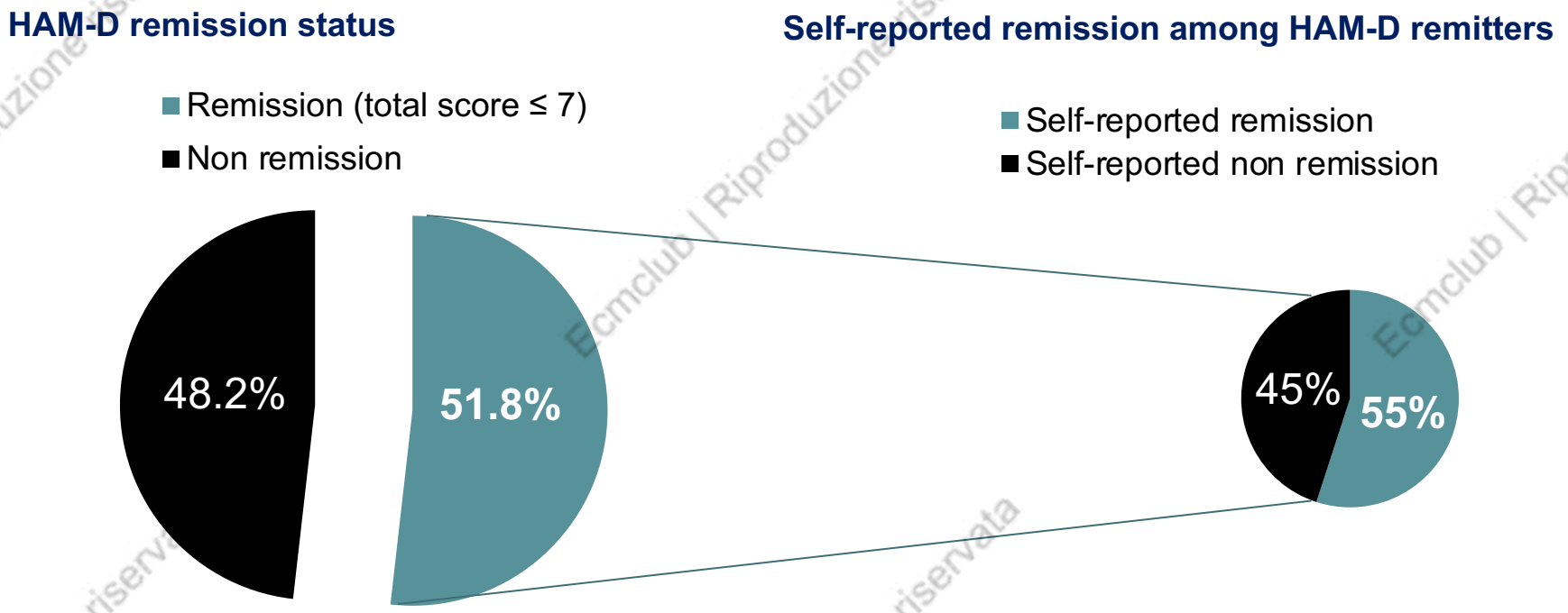


- MDD=major depressive disorder

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Health Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013; 2. Marazziti D, et al. Eur J Pharmacol. 2010;626(1):83–6; 3. Hammar A, Ardal G. Front Hum Neurosci. 2009;3:26. doi: 10.3389/neuro.09.026.2009; 4. Fehnel SE, et al. CNS Spectr. 2013;21:43–52

Depression has many unmet needs

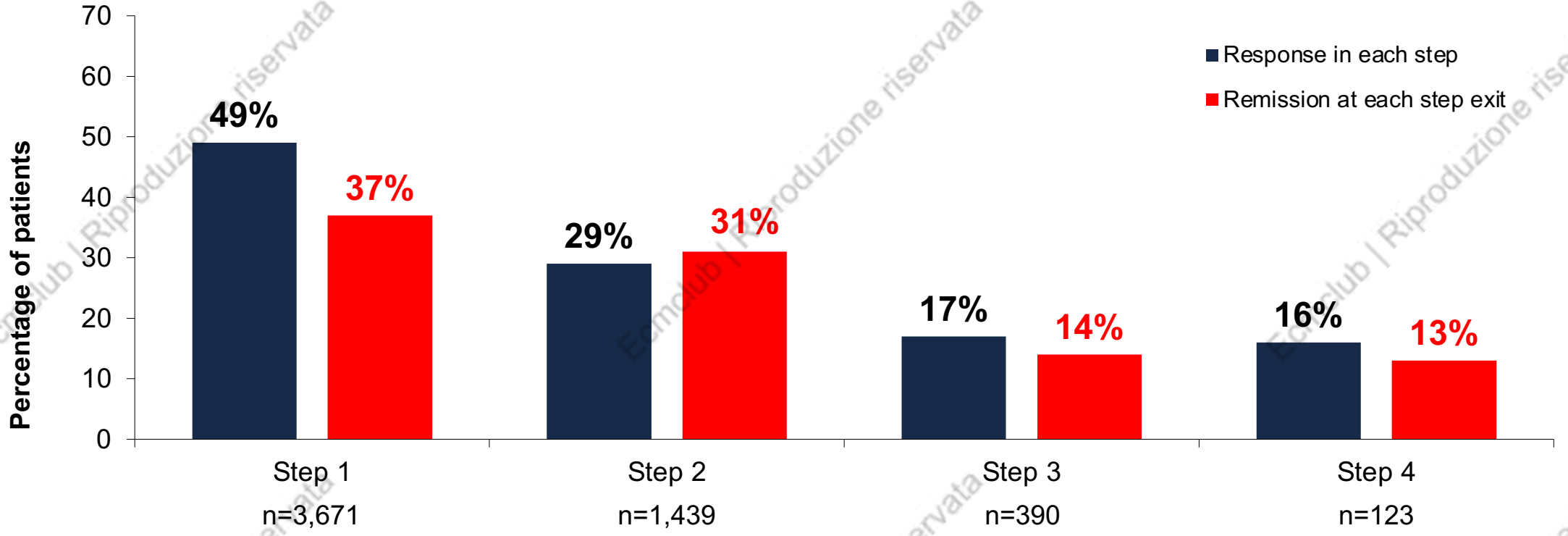
**Depressed outpatients who are in Remission according to HDRS*
Do Not Always consider themselves to be in Remission**



Zimmerman et al., 2012 J Clin Psychiatry 73:6
*HDRS: Hamilton Depression Rating Scale

About 50% of patients have a partial response to SSRI

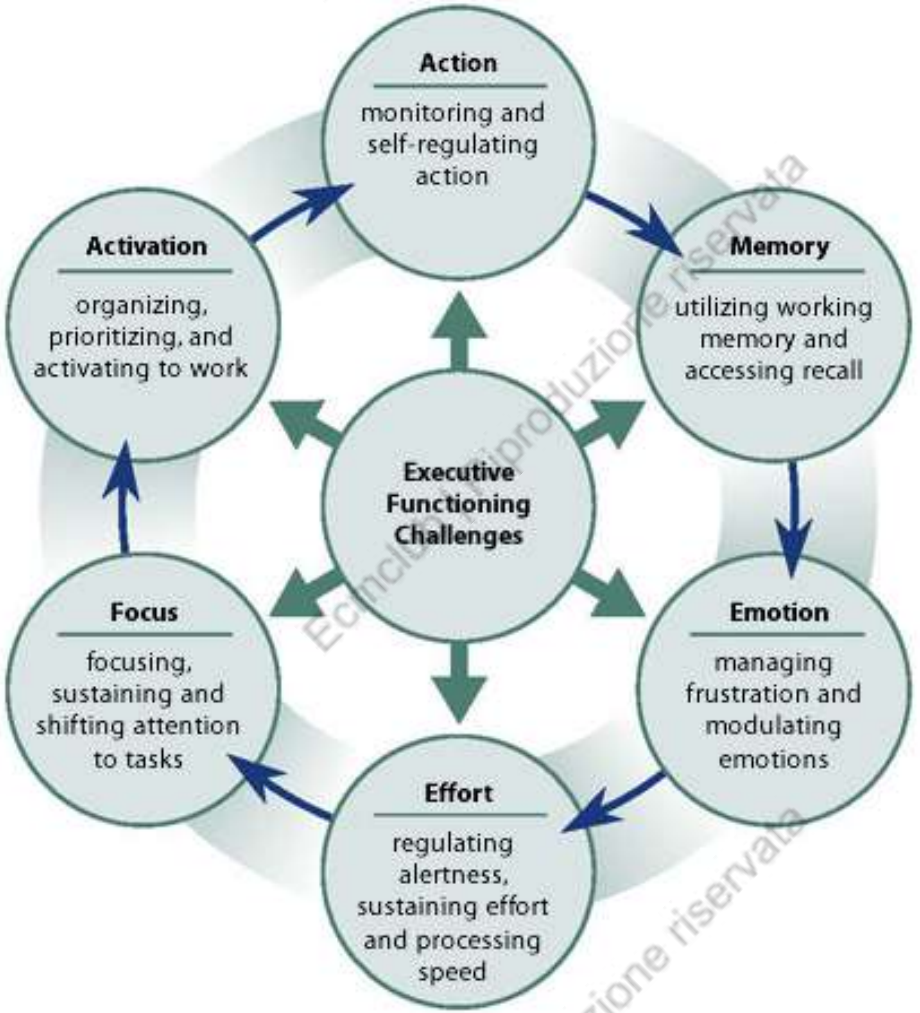
Patients achieving response (≥50% improvement in QIDS-SR16 score from baseline) at each treatment step in the STAR*D study[1]



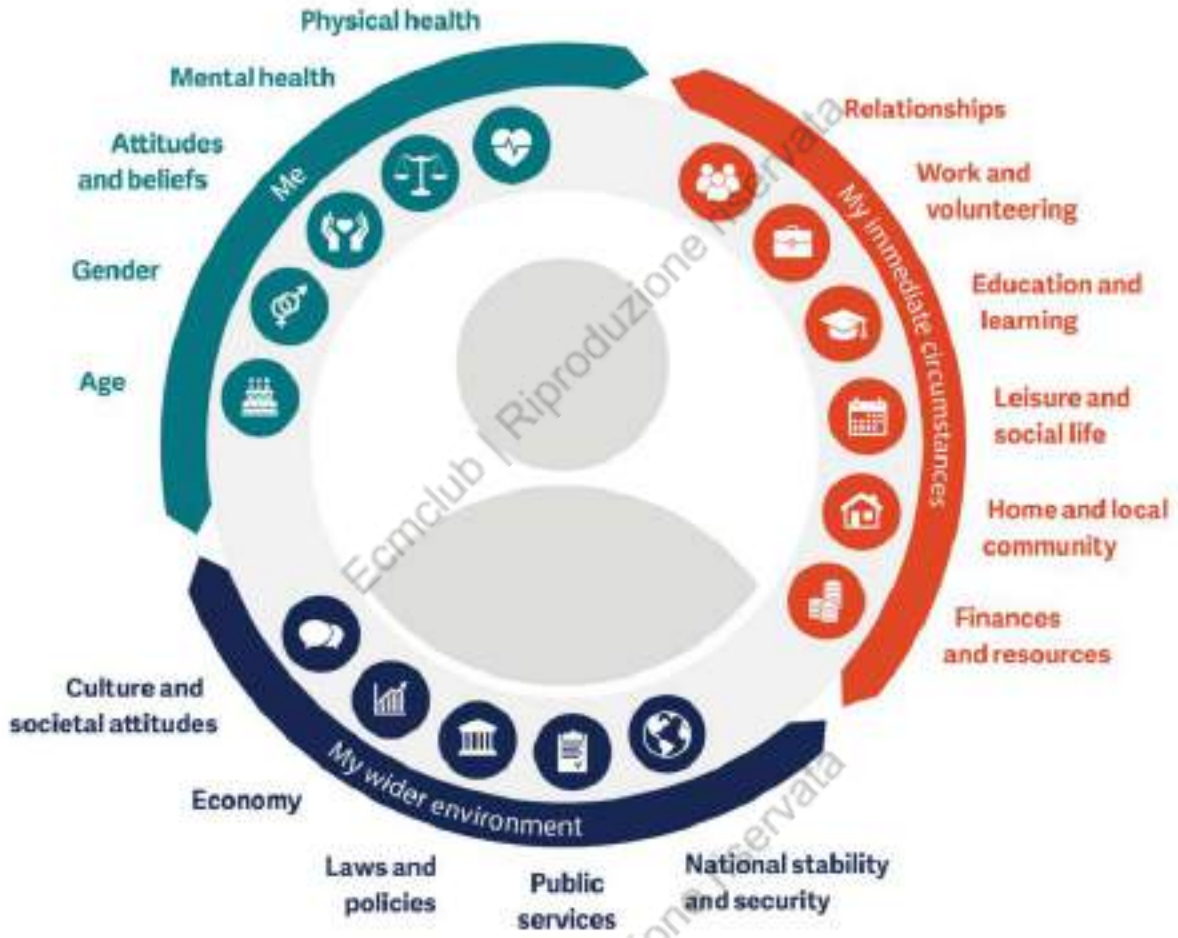
- QIDS-SR16=Self-reported 16 item Quick Inventory of Depressive Symptomatology; STAR*D=Sequenced Treatment Alternatives to Relieve Depression.
- Partial response is defined as 6–8 weeks at an adequate dosage and 25–50% decrease in MADRS or HAM-D score.[2]

1. Adapted from Rush AJ, et al. Am J Psychiatry. 2006;163:1905–17; 2. Adapted from Nierenberg AA et al. J Clin Psych. 2001;62(Suppl 16):5–9

Functioning

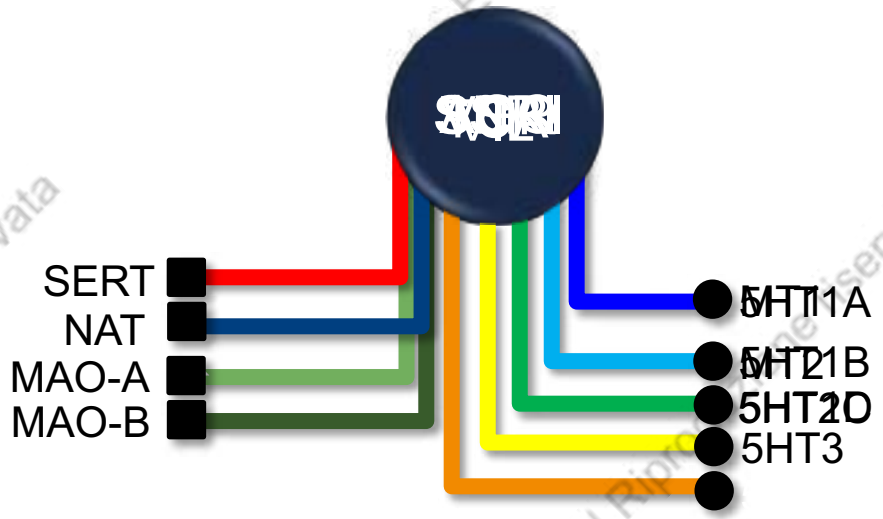


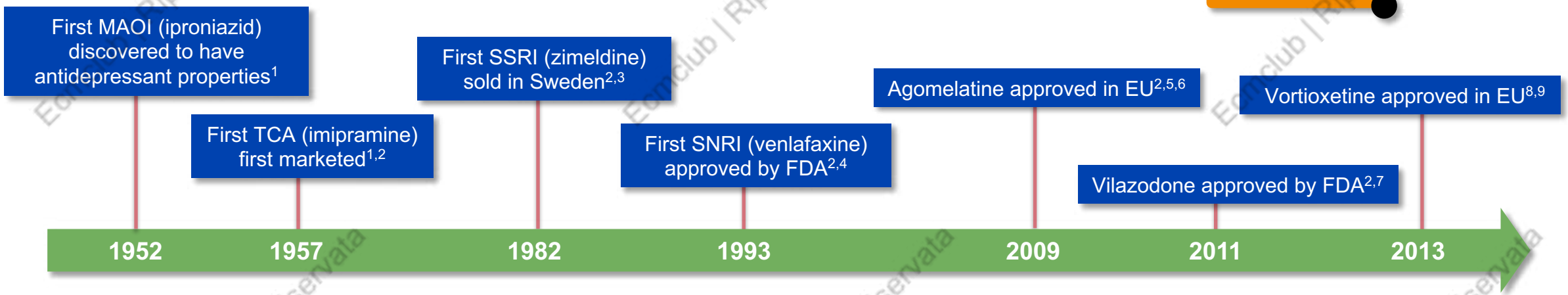
Quality of Life



Antidepressant drug development

Antidepressants with different MoAs have been developed





AGO=agomelatine; EU=European Union; FDA=Food and Drugs Agency; HT=hydroxytryptamine; MAOI=monoamine oxidase inhibitor; MOA=mechanism of action; NET=norepinephrine transporter; SERT=serotonin transporter; SNRI=serotonin–norepinephrine reuptake inhibitors; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant; VIL=vilazodone; VOR=vortioxetine

1.Ramachandraih CT, et al. Indian J Psychiatry. 2011;53(2):180–2; 2. Nutt DJ. J Psychopharmacol. 2009;23(4):343–5; 3. Fagius J, et al. J Neurol Neurosurg Psychiatry. 1985;48(1):65–9; 4. Sansone RA, et al. Innov Clin Neurosci 2014;11(3–4):37–42; 5. Fornaro M, et al. Curr Neuropharmacol. 2010;8(3):287–304.; 6. European Medicines Agency. Agomelatine Public Assessment Report. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000915/WC500046226.pdf; 7. Cruz MP. P T. 2012;37(1):28–31; 8. European Medicines Agency EMA/CHMP/630715/2013 October 2013. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002717/WC500153088.pdf; 9. Vortioxetine. EU Summary of Product Characteristics 2018. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002717/WC500159449.pdf All accessed August 2018

Treatment success in depression has evolved

Response
Many symptoms remain

Remission
Some symptoms may persist

Full functional recovery
Symptoms are essentially absent; patient returns to pre-morbid functional status

1970s

Reduction of symptoms (e.g. ≥50% of MADRS or HAM-D score)[2,3]

1990s

Commonly defined as MADRS score ≤10[2] or HAM-D17 score ≤7[1,3]

Current

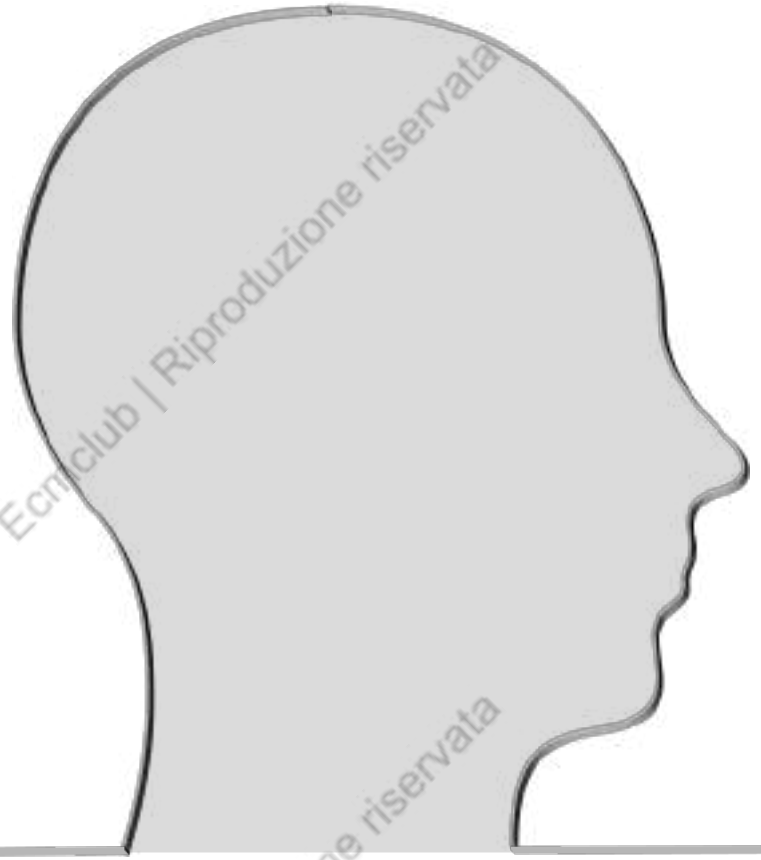
Direct questioning combined with a clinical impression to assess patient-specific functioning and quality of life[4]

Nearly half of depressed patients who achieve 'remission' do not consider themselves to be in remission[1,2]

MADRS=Montgomery-Åsberg Depression Rating Scale; HAM-D=Hamilton Depression Rating Scale

1. Zimmerman M, et al. J Clin Psychiatry 2012;73:790–5; 2. Hawley CJ, et al. J Affect Disord. 2002;72:177–84; 3. Nierenberg AA, DeCecco LM. J Clin Psychiatry. 2001;62(Suppl 16):5–9; 4. Saltiel PF, Silvershein DI. Neuropsychiatr Dis Treat. 2015;11:875–88

CONNECT Study outline



MDD outpatients in the USA and EU (n=602)

Age 18–65 years

MADRS ≥26

DSST <70

8-week RCT

- Duloxetine 60 mg
- Vortioxetine 10–20 mg
- Placebo

Primary outcome

- DSST

Key secondary outcomes

- MADRS
- UPSA

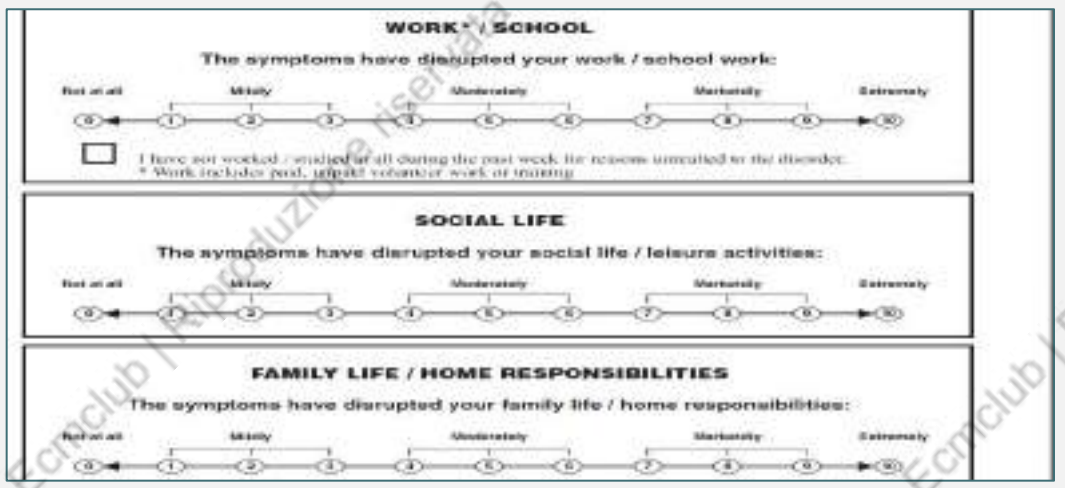
- MDD, major depressive disorder; MADRS, Montgomery-Åsberg Depression Rating Scale; DSST, Digit Symbol Substitution Test; RCT, randomised control trial; PDQ, Perceived Deficits Questionnaire

- Mahableshwarkar AR et al. Neuropsychopharmacology 2015;40:2025-37

Comparing Subjective vs Objective Results

Subjective assessment

Sheehan Disability Scale (SDS)



Objective measurement

University of California Performance-based Skills Assessment (UPSA)

VS.

UPSA: A Functional Assessment Scale

- Evaluates an individual's ability to perform everyday tasks considered necessary for independent functioning
- Uses role-playing situations to evaluate skills in five areas:

UPSA measures of everyday functioning	Finance	Communication	Household chores	Transportation	Planning/recreational activities
					
Examples:	Count money Read a bill Pay bills	Use telephone Reschedule a medical appointment	Prepare shopping list	Plan a bus trip	Plan for a trip to a water park

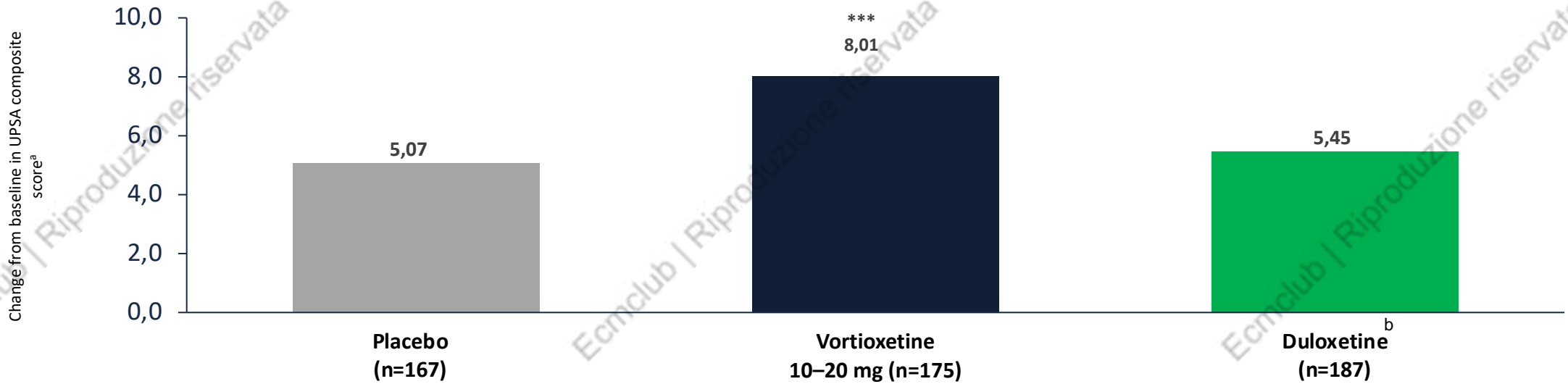
- Shown to be reliable and valid in research

UPSA, University of California Performance-Based Skills Assessment.

Patterson et al. *Schizophr Bull.* 2001;27:235-45.

Vortioxetine significantly improves everyday functioning

CONNECT study: change from baseline in UPSA composite score at Week 8 in patients with MDD[1]



UPSA measures of everyday functioning[2]

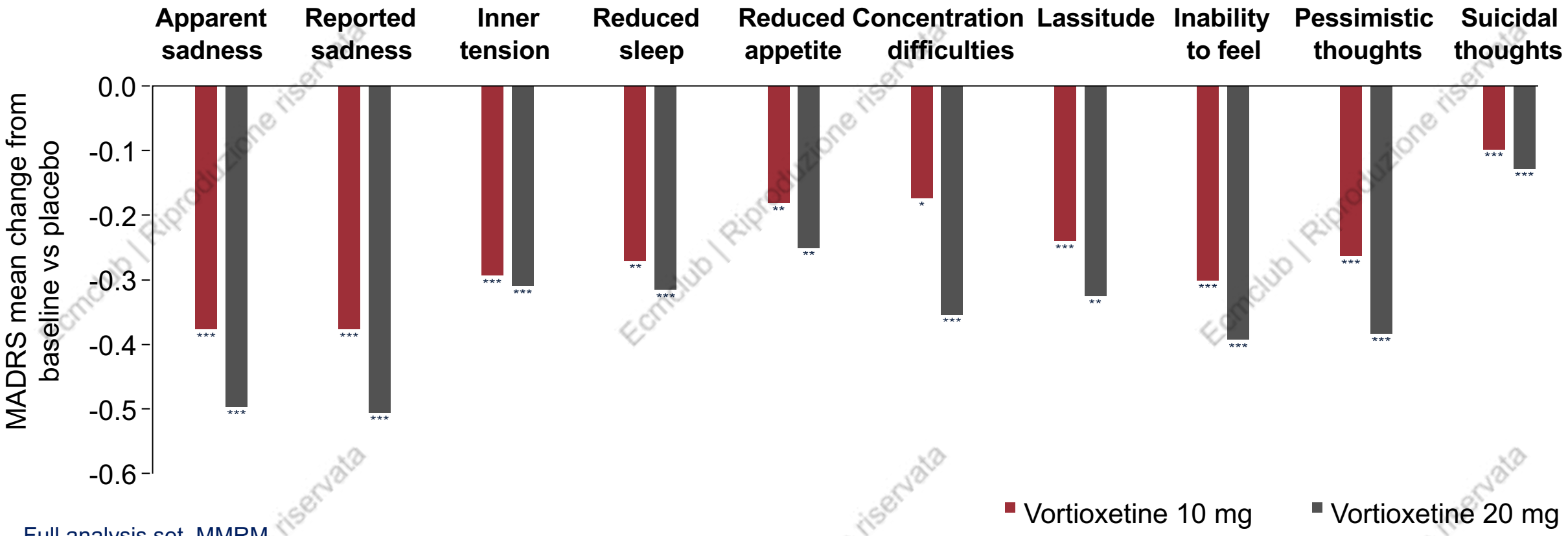
Household chores | Communication | Finance | Transportation | Planning / recreational activities

***p<0.001 vs placebo; [a]Composite of UPSA-Validation of Intermediate Measures and UPSA-Brief scores;
[b]duloxetine was included as active reference for study validation, not for comparison of effect sizes
UPSA, University of California at San Diego Performance-Based Skills Assessment; MDD, major depressive disorder

- 1. Mahableshwarkar AR et al. Neuropsychopharmacology 2015;40:2025-37;
  2. Patterson TL et al. Schizophr Bull 2001;27:235-45

Vortioxetine improved symptoms of MDD as measured by MADRS

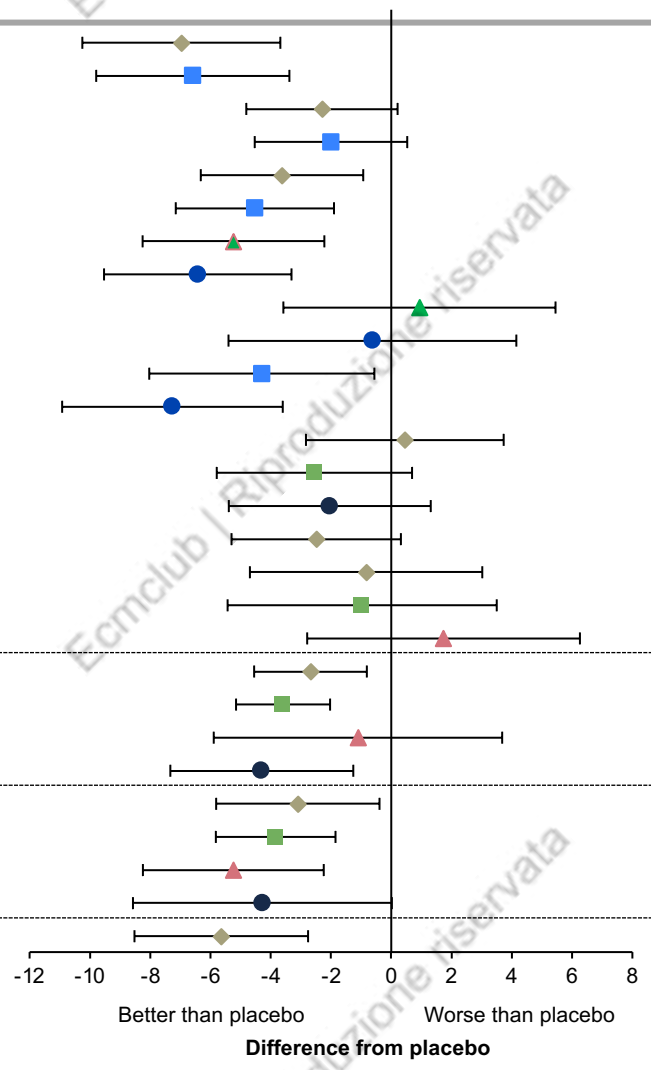
MADRS items in meta-analysis of 11 controlled studies (6/8 weeks)



- Full analysis set, MMRM
  *p<0.05; **p<0.01; ***p<0.001
  MADRS=Montgomery-Åsberg Depression Rating Scale; MDD=major depressive disorder; MMRM=mixed model for repeated measurements
- Adapted from Thase M, et al. Eur Neuropsychopharmacol. 2016;26(6):979–93

efficacious in depressed patients with high anxiety (HAM-A ≥20)

Ref	Study	Vortioxetine dose	Difference (95% CI)	n (VOR:PBO)
1	HLu 11492A	5 mg	-6.96 (-10.25, -3.68)	49:59
		10 mg	-6.58 (-9.79, -3.38)	53:59
2	HLu 11984A	5 mg	-2.30 (-4.81, 0.21)	89:89
		10 mg	-2.00 (-4.53, 0.53)	88:89
3	TAK 305	5 mg	-3.63 (-6.32, -0.93)	57:62
		10 mg	-4.53 (-7.15, -1.90)	65:62
4	HLu 13267A	15 mg	-5.24 (-8.25, -2.22)	71:71
		20 mg	-6.42 (-9.53, -3.31)	65:71
5	TAK 315	15 mg	0.93 (-3.58, 5.45)	44:42
		20 mg	-0.62 (-5.40, 4.15)	34:42
6	TAK 316	10 mg	-4.29 (-8.03, -0.56)	52:52
		20 mg	-7.26 (-10.92, -3.60)	57:52
7	TAK CCT-002	5 mg	0.45 (-2.83, 3.73)	54:58
		10 mg	-2.55 (-5.79, 0.69)	58:58
		20 mg	-2.04 (-5.39, 1.31)	51:58
8	TAK 303	5 mg	-2.49 (-5.30, 0.32)	123:110
9	TAK 304	5 mg	-0.83 (-4.69, 3.02)	43:49
10	TAK 317	10 mg	-0.97 (-5.43, 3.50)	57:60
		15 mg	1.73 (-2.79, 6.26)	56:60
11	Meta-analysis	5 mg	-2.68 (-4.55, -0.81)	415:427
		10 mg	-3.59 (-5.15, -2.03)	373:380
		15 mg	-1.11 (-5.89, 3.68)	171:173
		20 mg	-4.30 (-7.33, -1.26)	207:223
11	Meta-analysis non-US	5 mg	-3.10 (-5.81, -0.39)	249:268
		10 mg	-3.83 (-5.82, -1.85)	264:268
		15 mg	-5.24 (-8.24, -2.24)	71:71
		20 mg	-2.27 (-8.57, 0.02)	116:129
12	HLu 12541A	5 mg	-5.64 (-8.52, -2.76)	75:61

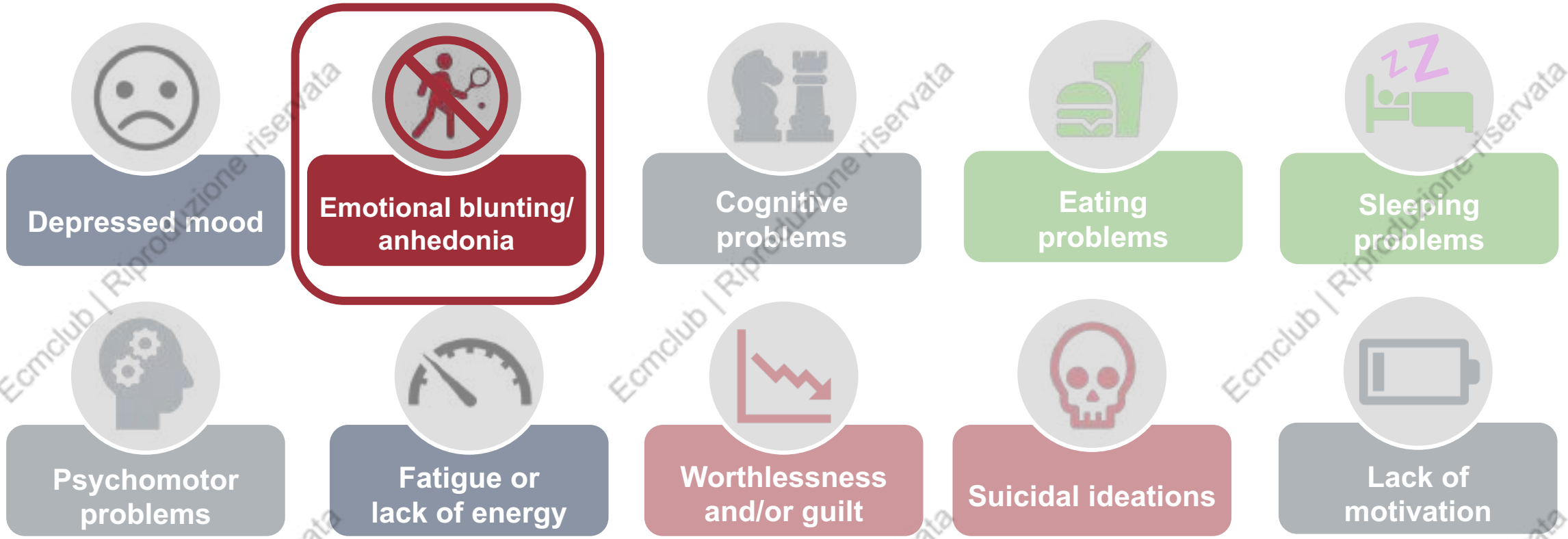


CI=confidence interval; PBO=placebo; VOR=Brintellix®

Full reference citations are available in the slide notes.
1. Alvarez et al. 2012; 2. Baldwin et al. 2012;
3. Heningsberg et al. 2012; 4. Boulenger et al. 2014;
5. Mahableswarkar et al. APA 2013a; 6. Jacobsen et al. APA 2013;
7. CHMP. 2013; 8. Jain et al. 2013; 9. Mahableshwarkar et al. 2013;
10. Mahableshwarkar et al. APA 2013b; 11. Baldwin et al. 2014; 12. Katona et al. 2012

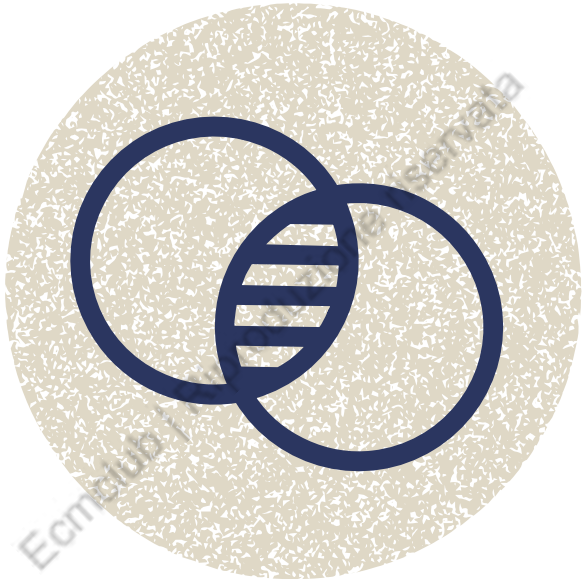
Partial response implies residual symptoms

Residual symptoms may include:[1,2]



1. Conradi HJ, et al. Psychol Med. 2011;41:1165–74; 2. Culpepper L, et al. Am J Med. 2015;128:S1–S15.

What is anhedonia?



Emotional blunting **phenotypically** overlaps with anhedonia[1,2]

Anhedonia is described as the **inability or reduced ability to experience pleasure**, having 'lack of drive' or reduced motivation[3]

1. Loas G et al. Compr Psychiatry 1994;35:366-72;
2. Cao B et al. Front Psychiatry 2019;10:17;
3. Franken IH et al. J Affect Disord 2007;99:83-9

Anhedonia is a common symptom of MDD

Anhedonia is reported in **~75%** of **patients**[1]

50–65% of **adolescent patients** with MDD reported experiencing anhedonia[2,3]

MDD, major depressive disorder

1. Franken IH et al. J Affect Disord 2007;99:83-9;
2. Orchard F et al. Child Adolesc Ment Health 2017;22:61-8;
3. Goodyer IM et al. Lancet Psychiatry 2017;4:109-19

What is emotional blunting?

Emotional blunting is described as the '**numbing**' or '**flattening**' of emotions, as well as **emotional indifference** or **reduced emotional responsiveness** such as **not caring**, **being emotionally detached**, **having a reduction in positive emotions** and a **general reduction in emotions**[1]

- Blunting is assumed to relate to **serotonergic effects** on the frontal lobes and / or serotonergic modulation of mid-brain dopaminergic systems, which project to the prefrontal cortex[2]
- Blunting may be a consequence of **reduced dopamine or reduced glutamatergic activity**[2]

1. Goodwin GM et al. J Affect Disord 2017;221:31-5;
2. Sansone RA, Sansone LA. Psychiatry (Edgmont) 2010;7:14-8

Emotional blunting is common in patients with MDD

Emotional blunting is a **prominent complaint of recovering patients** with MDD and is a **common reason** for patients with MDD **to stop treatment**[1]

Nearly half of the participants in a recent survey **of 669 patients** with MDD **receiving antidepressants reported emotional blunting** as a side effect[2]

- It is also associated with a poorer quality of remission[2]

MDD, major depressive disorder

1. Rosenblat JD et al. J Affect Disord 2019;243:116-20;
2. Goodwin GM et al. J Affect Disord 2017;221:31-5

Consequences of emotional blunting

Emotional blunting can extend to reductions in

- Sexual interest
- Motivation in the workplace

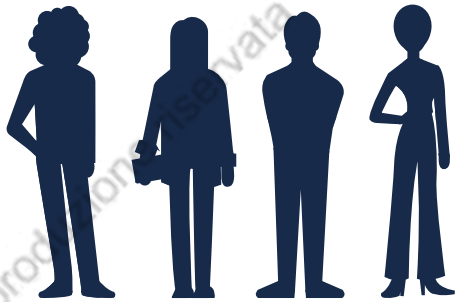
Significantly impacting on patient QoL[1]

QoL, quality of life

1. Price J, Goodwin GM. Medicographia 2009;31:152-6

The effect of emotional blunting on treatment adherence

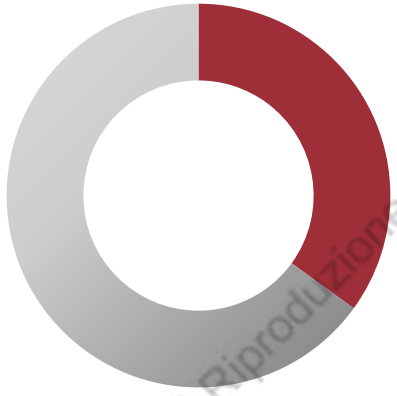
The effect of emotional blunting on decision making can ultimately affect treatment adherence, increasing the risk of relapse[1]



In a study of

316

patients with MDD



35%

of patients discontinued treatment due to emotional blunting[2]

MDD, major depressive disorder

1. Sirey JA et al. JAMA Psychiatry 2017;74:1129-35;
2. Rosenblat JD et al. J Affect Disord 2019;243:116-20

Evaluating the effects of antidepressant treatment on emotional blunting and anhedonia

- The first study examining emotional blunting under double-blind conditions found that components of emotional blunting were not only present but very common at baseline[1]
- The severity of these components was reduced after treatment with agomelatine or escitalopram, with a greater reduction observed for agomelatine vs escitalopram[1]
- Moreover, some antidepressants have been shown to help treat anhedonia in MDD, which generally phenotypically overlaps with emotional blunting
  - An outpatient, open-label, real-world study, evaluating the effectiveness of agomelatine on anhedonia using the SHAPS 14-item self-reported questionnaire, showed significant improvement in the severity of anhedonia after 8 weeks of treatment[2]
  - An open-label study evaluating the effects of vortioxetine on anhedonia found that vortioxetine significantly improved SHAPS and MADRS measures of anhedonia within 8 weeks[3]

The results of these studies imply that emotional blunting, along with anhedonia, is a component of MDD that improves with effective treatment

MDD, major depressive disorder; SHAPS, Snaith–Hamilton Pleasure Scale; MADRS, Montgomery-Åsberg Depression Rating Scale

1. Corruble E et al. Int J Neuropsychopharmacol 2013;16:2219-34;
2. Gargoloff PD et al. Hum Psychopharmacol 2016;31:412-8;
3. Cao B et al. Front Psychiatry 2019;10:17

A study on Emotional Blunting

Internet-based survey

~20 minutes

Panel of English-speaking people aged ≥18

Screened for diagnosis by medical professional

Invites sent*

N=4,194

N=2,255

N=1,517

OQuESA

- Emotional blunting was measured using the Oxford Questionnaire on the Emotional Side-effects of Antidepressants (OQuESA)[2]
- Self-reported questionnaire measuring on a 5-point scale responses to question from three sections:
  - Current experience with EB
  - Recollection of emotional state prior to treatment
  - Perceived link between treatment and EB
- **Higher OQuESA score = greater degree of EB**

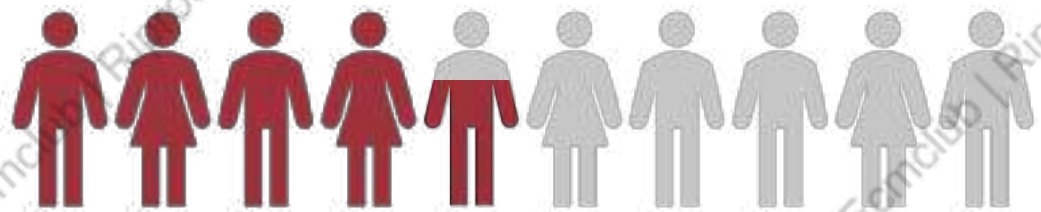
*Patients or controls receiving additional psychotropic medications (antipsychotics, mood stabilisers, or antiepileptics) were excluded from the survey.
HAD-D=Hospital Anxiety and Depression Scale – depression sub-score; Tx=treatment.

1. Goodwin GM, et al. *J Affect Disord.* 2017;221:31–35; 2. Price J, et al. *J Affect Disord.* 2012; 140:66–74.

Emotional blunting is reported by nearly half of depressed patients on antidepressants

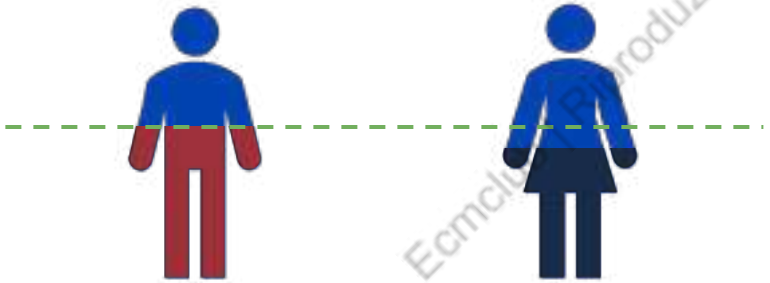
46%
(n=310/669)

of patients being treated with antidepressants experienced **emotional blunting***



The experience of EB was slightly more frequent in **men (52%)** than **women (44%)**

The experience of EB was slightly more frequent in **men (52%)** than **women (44%)**



*91 patients who were receiving >1 antidepressant were excluded to provide a more homogenous population of patients with MDD on monotherapy.
EB=emotional blunting; HAD-D= Hospital Anxiety and Depression Scale – depression sub-score.
Adapted from Goodwin GM, et al. *J Affect Disord.* 2017;221:31–35.

Prevalence of emotional blunting by antidepressants

Antidepressant	Patients receiving antidepressant, n	Patients with emotional blunting, n (%)
Citalopram	127	58 (46%)
Venlafaxine	105	48 (46%)
Fluoxetine	98	46 (47%)
Sertraline	80	36 (45%)
Paroxetine	58	25 (43%)
Escitalopram	53	23 (43%)
Bupropion	40	13 (33%)
Duloxetine	36	27 (75%)
Amitriptyline	17	8 (47%)
Mirtazapine	17	7 (42%)
Desvenlafaxine*	9	5 (56%)
Others	29	14 (48%)
Total	**669**	**310 (46%)**

There was **no statistically significant difference** between antidepressants, although there was a trend towards fewer report with bupropion

***Desvenlafaxine is NOT approved for use in MDD in China.** Citalopram is indicated for the treatment of MDD in adults. Escitalopram is indicated for the treatment of depression and the treatment of panic disorder with or without agoraphobia. Prescribing information for escitalopram and vortioxetine can be found at the end of this slide-deck, and further information can be found in the respective SmPCs, available on your iPad. HAD-D=Hospital Anxiety and Depression Scale – depression sub-score. Adapted from Goodwin GM, et al. J Affect Disord. 2017;221:31–35.

Anhedonia in MDD

- Emotional blunting phenotypically overlaps with anhedonia,[1,2] a common symptom of MDD reported in ~75% of patients[3]
- Anhedonia has been implicated in disturbances of central dopaminergic, mesolimbic, and mesocortical reward circuit pathways[4]
- Anhedonia and impaired reward circuit pathways are associated with a poorer prognosis and suboptimal treatment response[5]
- Given its multimodal mechanism of action as well as the cognitive effects, vortioxetine may contribute towards alleviating anhedonia[2]

MDD=major depressive disorder.

1. Loas G, et al. Compr Psychiatry. 1994;35:366–72; 2. Cao B, et al. Front Psychiatry. 2019;10. DOI: 10.3389/fpsyt.2019.00017; 3. Franken IH, et al. J Affect Disord. 2007;99:83–9; 4. Pan Z, et al. Curr Pharm Des. 2017;23:2065–72; 5. Buckner JD, et al. 2008;159:25–30.

Effects of vortioxetine on anhedonia

- 18–65 years old
- DSM-5 defined MDD with at least moderate symptom severity (i.e. MADRS total score ≥20)
- History of ≥1 prior diagnosed MDE
- Outpatient of a psychiatric setting

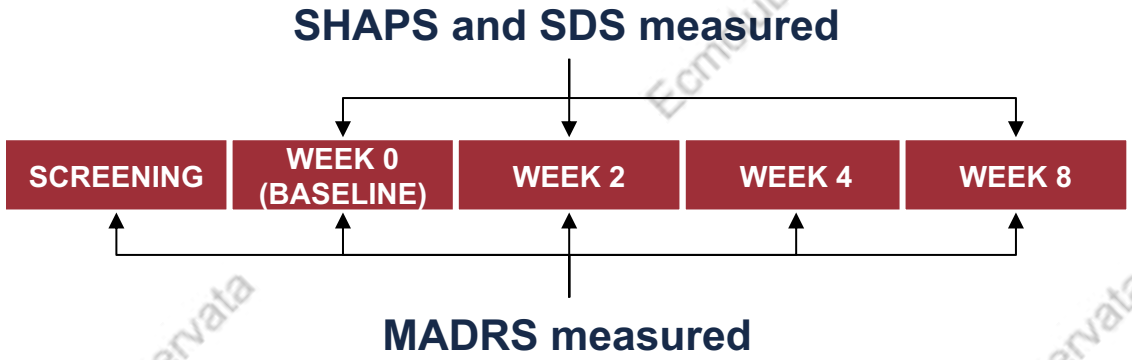
95 patients were analysed

- Open-label vortioxetine
- 10–20 mg/day for 8 weeks, flexibly dosed

Aim: To determine whether vortioxetine improved measures of anhedonia and to what extent improvements in **anhedonia** correlate with overall **function** and health-related **quality of life***

Primary outcome: Change in anhedonia measured by baseline to endpoint changes in SHAPS and MADRS anhedonia factor*

Secondary outcomes: Functional impairment via SDS and health-related quality of life via WHO-5*



*Referring to a post-hoc analysis of the primary study that sought to evaluate the sensitivity to change of the THINC-integrated tool in MDD (NCT03053362).
DSM-5=Diagnostic and Statistical Manual of Mental Disorders, MADRS=Montgomery and Asberg Depression Rating Scale, MDD=major depressive disorder, MDE=major depressive episode, SDS=Self-rated Depression Scale, SHAPS=Snaith-Hamilton Pleasure Scale, WHO-5=World Health Organisation – Five Well-being. Index. Adapted from Cao B, et al. Front Psychiatry. 2019;10. DOI: 10.3389/fpsyt.2019.00017.

Snaith-Hamilton-Pleasure-Scale (SHAPS)

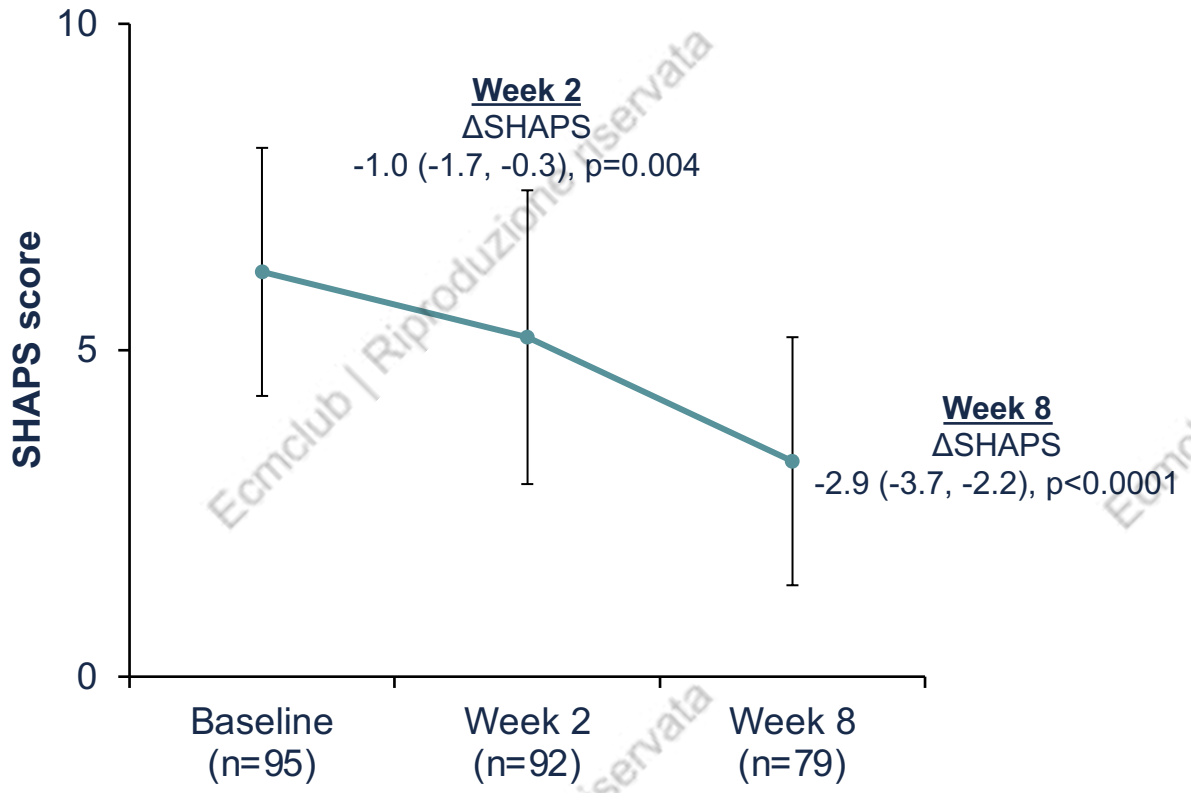
The Snaith-Hamilton-Pleasure-Scale (**SHAPS**) is a 14-item, self-reported scale evaluating anhedonia for neuropsychiatric disorders.

- I would enjoy my favourite television or radio program
- I would enjoy being with family or close friends
- I would find pleasure in my hobbies and pastimes
- I would be able to enjoy my favourite meal
- I would enjoy a warm bath or refreshing shower
- I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread
- I would enjoy seeing other people's smiling faces
- I would enjoy looking smart when I have made an effort with my appearance
- I would enjoy reading a book, magazine or newspaper
- I would enjoy a cup of tea or coffee or my favourite drink
- I would find pleasure in small things; e.g., bright sunny day, a telephone call from a friend
- I would be able to enjoy a beautiful landscape or view
- I would get pleasure from helping others
- I would feel pleasure when I receive praise from

Adapted from Snaith RP, et al. Br J Psychiatry. 1995;167:99–103.

Vortioxetine significantly improved anhedonia as evidenced by improvements in SHAPS scores

Change in SHAPS scores with treatment of vortioxetine

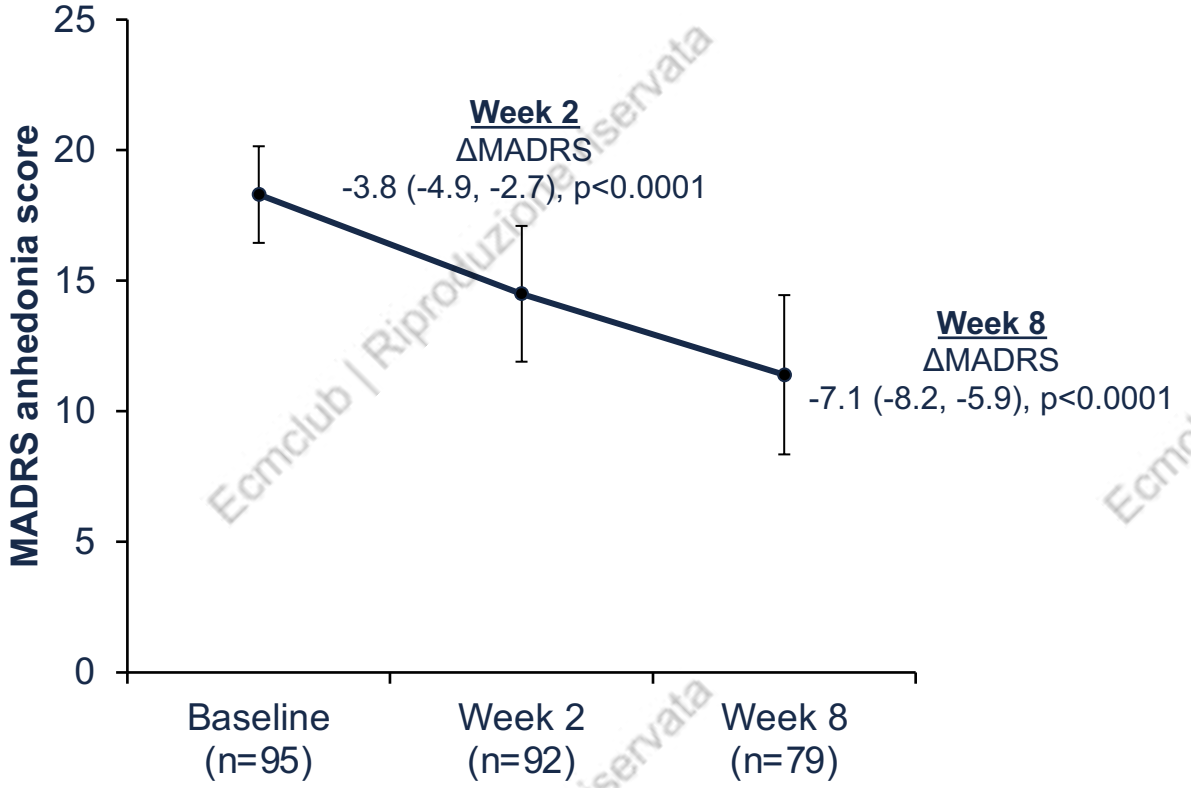


SHAPS score is a pre-planned secondary outcome measure of the primary study as confirmed by study investigators. SHAPS=Snaith-Hamilton Pleasure Scale.

Adapted from Cao B, et al. Front Psychiatry. 2019;10. DOI: 10.3389/fpsyt.2019.00017.

Vortioxetine significantly improved anhedonia (MADRS anhedonia factor scores)

Change in MADRS anhedonia factor scores with treatment of vortioxetine



MADRS=Montgomery and Asberg Depression Rating Scale.

Adapted from Cao B, et al. Front Psychiatry. 2019;10. DOI: 10.3389/fpsyt.2019.00017.

Improvements in anhedonia correlated with improvements in general function and quality of life

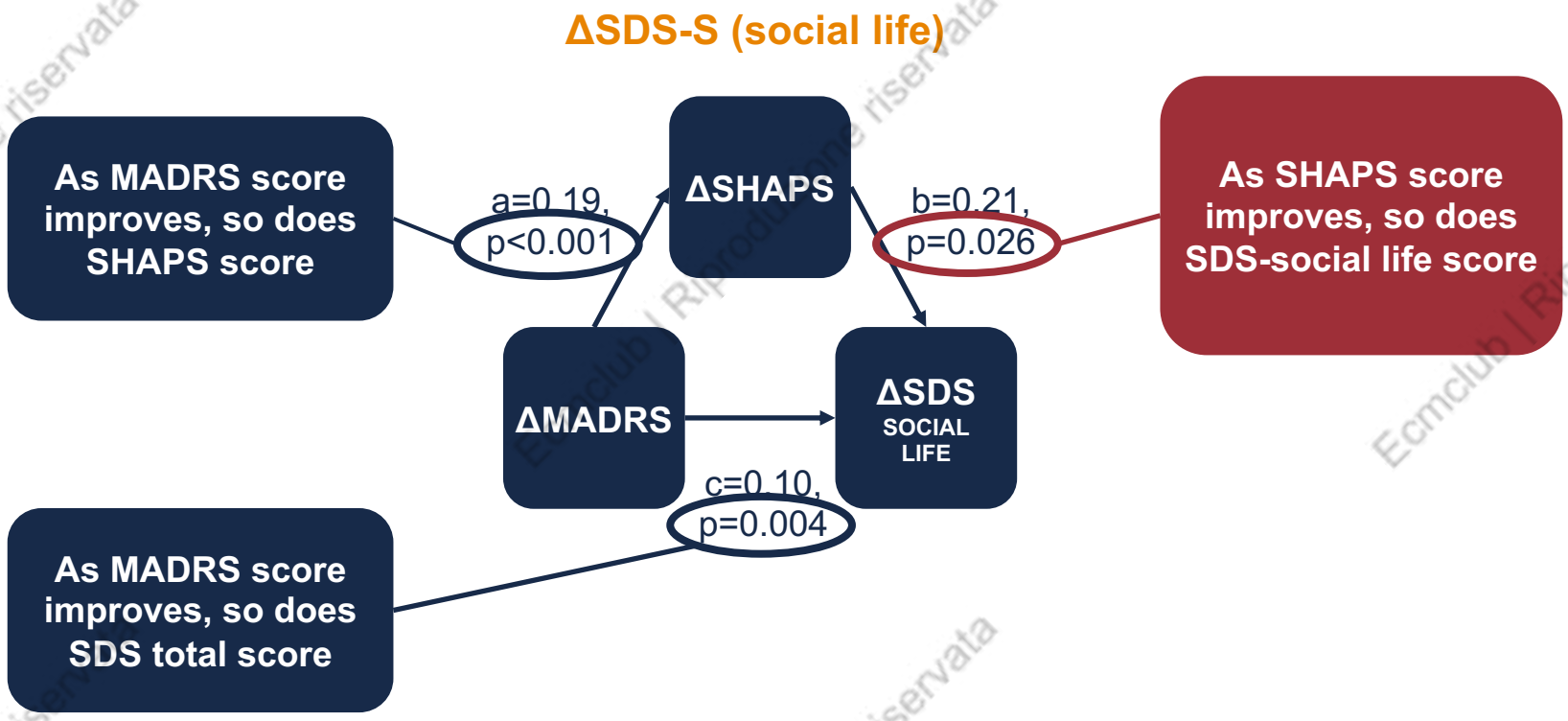
Correlations of the endpoint changes between functional impairment, well-being, and anhedonia from baseline

Correlations	SDS total score		SDS work		SDS social life		SDS family life		WHO-5	
	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value
MADRS total score	0.527	<0.001	0.422	<0.001	0.46	<0.001	0.486	<0.001	-0.604	<0.001
SHAPS score	0.392	<0.001	0.309	0.006	0.403	<0.001	0.365	0.001	-0.336	0.002
MADRS anhedonia factor score	0.511	<0.001	0.423	<0.001	0.41	<0.001	0.507	<0.001	-0.570	<0.001

MADRS=Montgomery and Asberg Depression Rating Scale, SDS=Self-rated Depression Scale, SHAPS=Snaith-Hamilton Pleasure Scale, WHO-5=World Health Organisation – Five Well-being. Adapted from Cao B, et al. Front Psychiatry. 2019;10. DOI: 10.3389/fpsyt.2019.00017.

Alleviation of anhedonia may mediate improvement in social functioning

Mediation analysis to estimate indirect effects of anhedonia improvement (ΔSHAPS) in the improvement of depressive symptoms (ΔMADRS) and function (ΔSDS)



a,b and c are path coefficients. MADRS=Montgomery and Asberg Depression Rating Scale, SDS=Self-rated Depression Scale, SHAPS=Snaith-Hamilton Pleasure Scale. Adapted from Cao B, et al. Front Psychiatry. 2019;10. DOI: 10.3389/fpsyt.2019.00017.

Interventional, open-label, flexible-dose study of vortioxetine on emotional blunting in patients with MDD with partial response to SSRI / SNRI treatment

COMPLETE clinical study

Study rationale and aim

AIM

PATIENTS

DESIGN

OBJECTIVES & ASSESSMENTS

Rationale

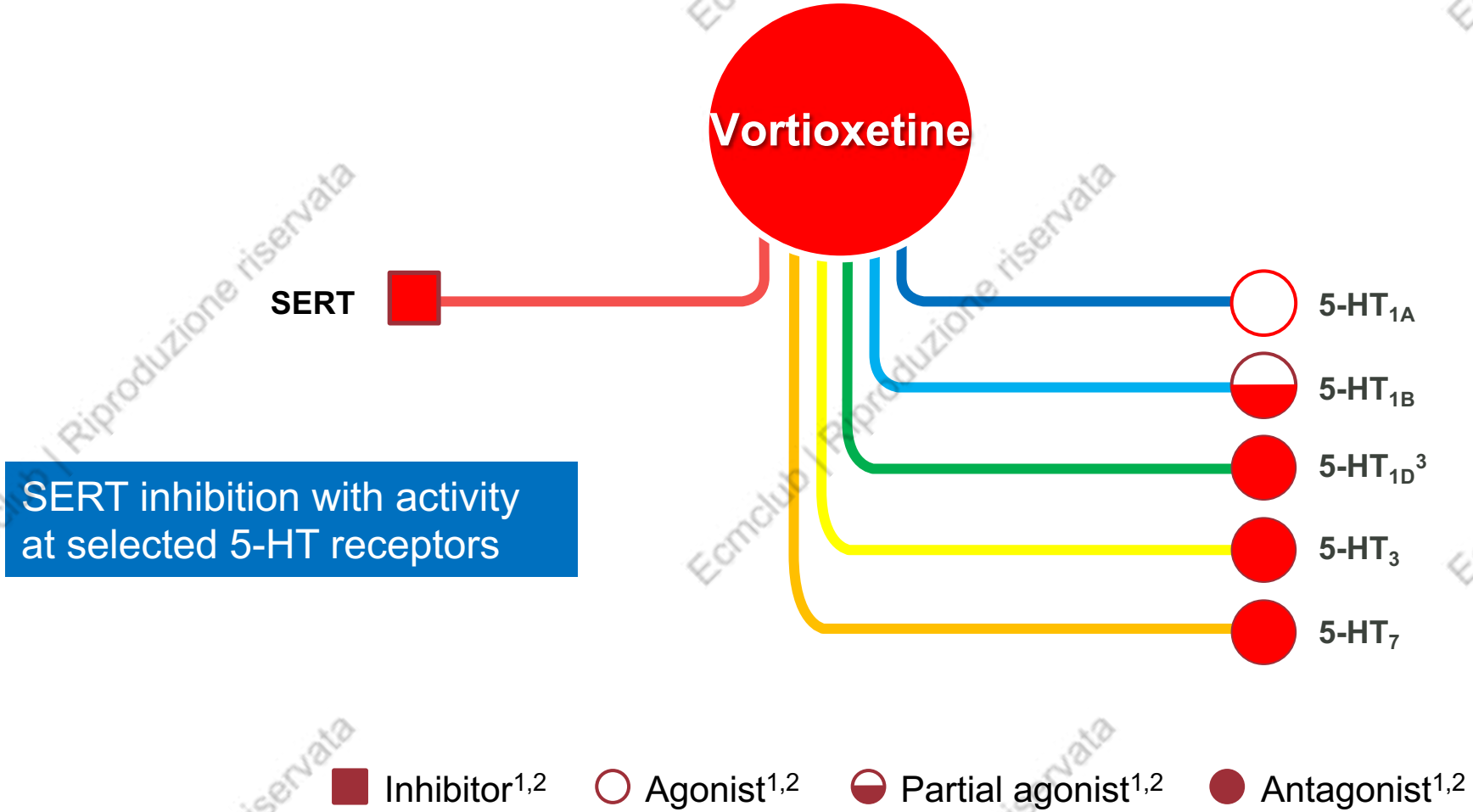
- **Approximately 50% of patients treated with SSRIs or SNRIs report suffering from emotional blunting**[1]
- Blunted emotions result in real **clinical and functional consequences** for patients' social, family and work lives[2]
- If patients experience blunted emotions with their SSRI or SNRI treatment, **alternative antidepressants** should be explored
- Based on the mechanism of action of vortioxetine, in particular modulation of 5-HT_3 and the downstream positive effect on dopamine, **vortioxetine may have a positive effect on emotional blunting**[3]

This study evaluated the effectiveness of 10–20 mg/day vortioxetine on emotional blunting in patients with MDD and a partial response to SSRI / SNRI[4]

SSRI, selective serotonin reuptake inhibitor;
SNRI, serotonin–noradrenaline reuptake inhibitor; MDD, major depressive disorder

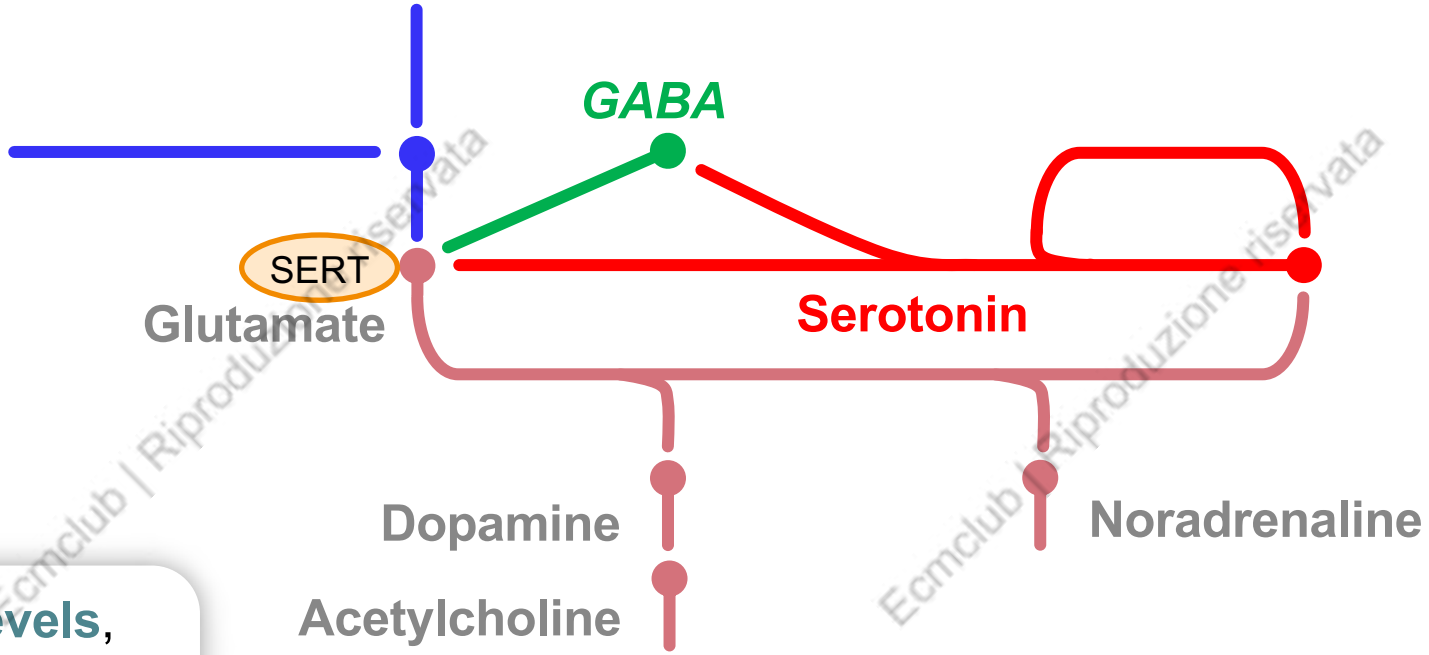
1. Goodwin GM et al. J Affect Disord 2017;221:31-5;
2. Price J et al. Br J Psychiatry 2009;195:211-7;
3. Sanchez C et al. Pharmacol Ther 2015;145:43-57;
4. Fagiolini A et al. Poster P.332 presented at ECNP 2020

Vortioxetine is a multimodal antidepressant



- HT=hydroxytryptamine; SERT=serotonin transporter
- 1. Bang-Andersen B, et al. J Med Chem. 2011;54(9):3206–21; 2. Sanchez C, et al. Pharmacol Ther. 2015;145:43–57 3. Vortioxetine. EU Summary of Product Characteristics 2018. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002717/WC500159449.pdf Last accessed August 2018

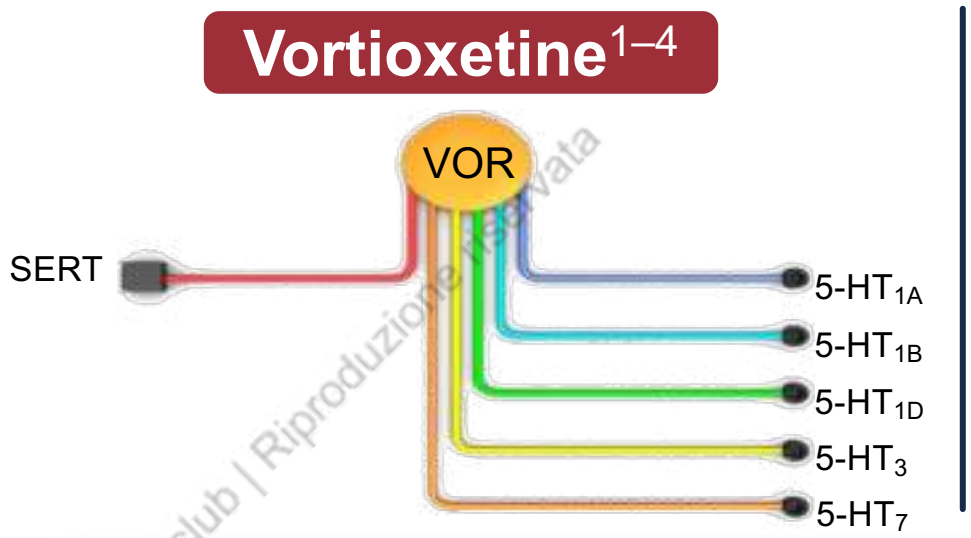
SSRIs and neurotransmission

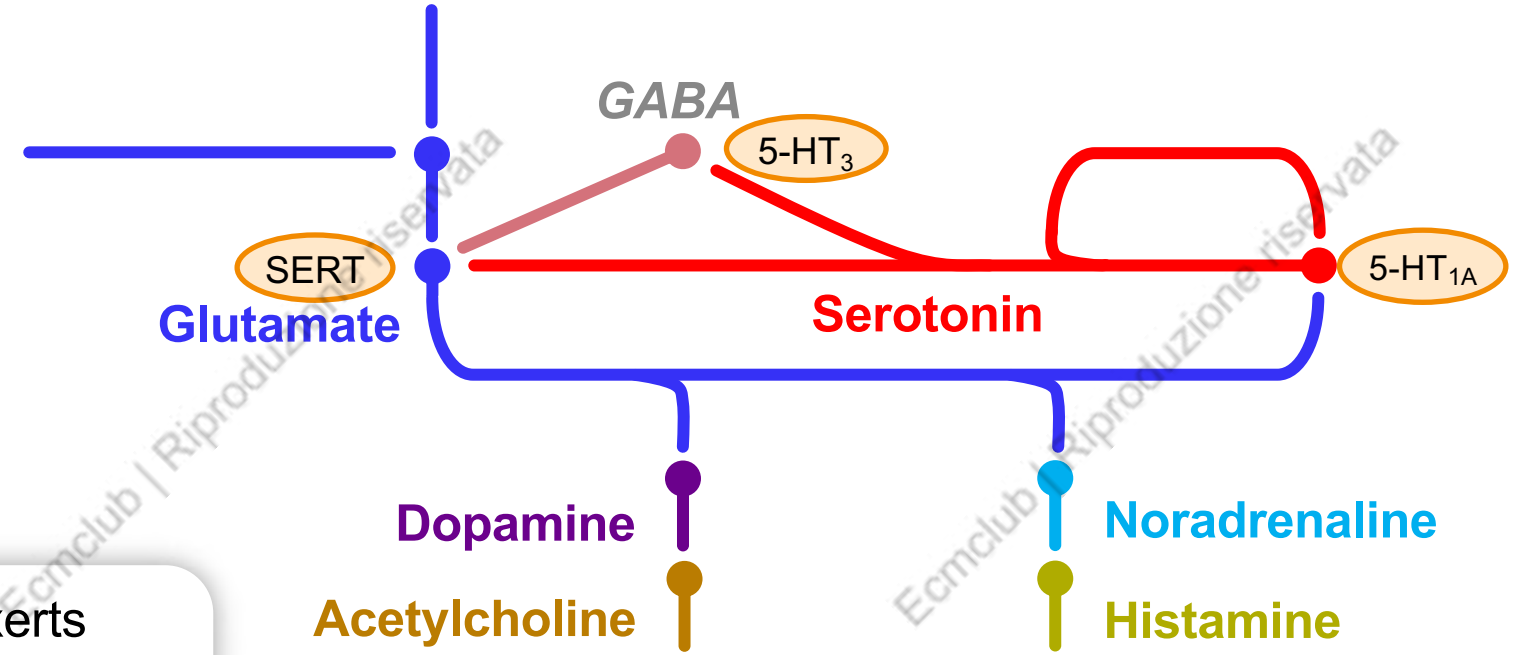


SSRIs cause a **global elevation in 5-HT levels**, and the indiscriminate activation of 5-HT receptors that dampens downstream neurotransmission

- GABA=gamma-aminobutyric acid; HT=hydroxytryptamine; SERT=serotonin transporter; SSRI-serotonin reuptake inhibitor
- The precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear and caution should be applied when extrapolating animal data directly to humans.
- 1. El Mansari M, et al. CNS Neurosci Ther. 2010;16(3): e1–e17; 2. West CHK, et al. Int J Neuropsychopharmacol. 2011;14(2):201–10; 3. Szabo ST, et al. Int J Neuropsychopharmacol. 2000;3(1):1–11; 4. Kawahara Y, et al. Psychopharmacology (Berl). 2007;194(1):73–81; 5. Dremencov E, et al. Curr Drug Targets. 2009; 10(11):1061–8; 6. DeGroot A, Nomikos GG. Neuropsychopharmacology. 2005;30(2):391–400; 7. Jackson D, et al. Brain Res 1988;457(2):259–66; 8. Komlósi G, et al. J Neurosci. 2012; 32(46):16369–78.

Vortioxetine and neurotransmission

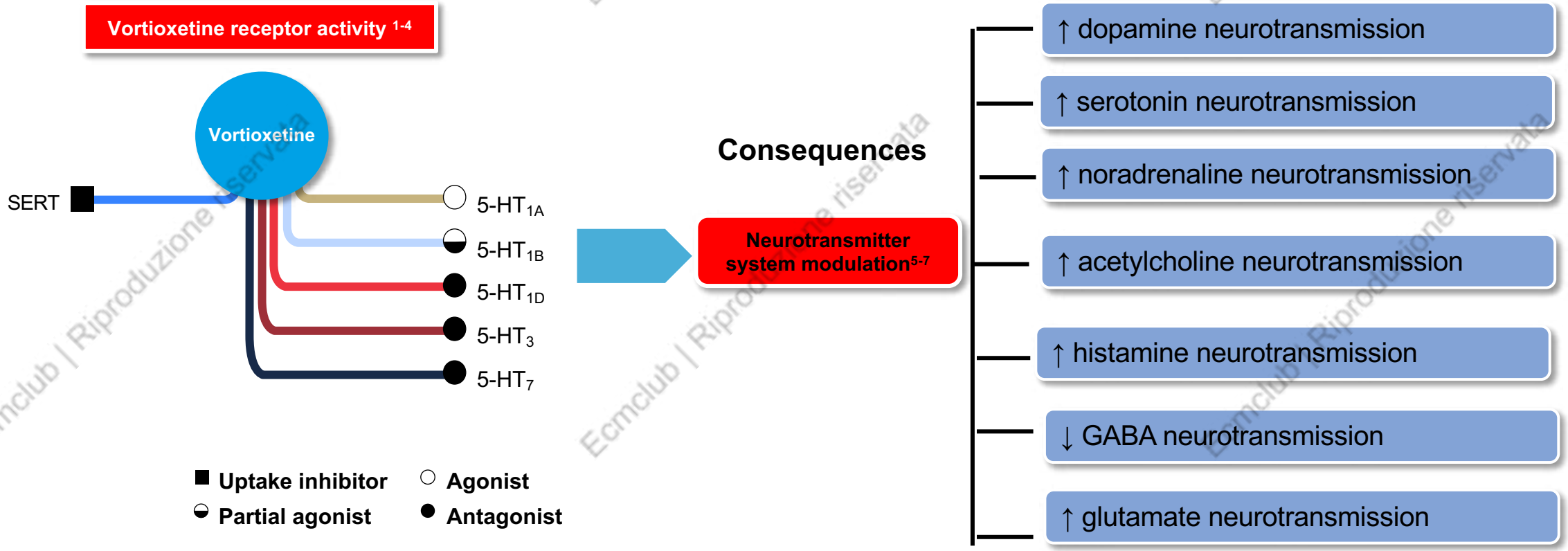




Vortioxetine's multimodal pharmacology exerts **distinct effects across neural pathways** associated with mood and cognition, including enhanced glutamate signalling[1–4]

- GABA=gamma-aminobutyric acid; HT=hydroxytryptamine; SERT=serotonin transporter; SSRI-serotonin reuptake inhibitor; VOR=vortioxetine
- The precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear and caution should be applied when extrapolating animal data directly to humans.
- 1. Guilloux JP, et al. Neuropharmacology. 2013;73:147–159; 2. Pehrson AL, et al. Eur Neuropsychopharmacol. 2013;23(2):133–145; 3. Mørk A, et al. Pharmacol Biochem Behav. 2013;105:41–

Vortioxetine Pharmacologic Profile



In the forebrain, the precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear and caution should be applied when extrapolating animal data directly to man.

5-HT=serotonin; GABA=gamma-aminobutyric acid; SERT=serotonin transporter.

1. Bang-Anderson B, et al. *J Med Chem.* 2011;54:3206-3221; 2. Mørk A, et al. *J Pharmacol Exp Ther.* 2012;340:666-675; 3. Vortioxetine EPAR; 4. Westrich L, et al. Poster at IFMAD 2012; 5. Mørk A, et al. Poster at ECNP 2011; 6. Pehrson A, et al. Poster at ECNP 2013; 7. Mørk A, et al. Poster at APA 2013; 8. Alvarez E, et al. *Int J Neuropsychopharmacol.* 2012;15:589-600; 9. Katona C, et al. *Int Clin Psychopharmacol.* 2012;27:215-223; 10. Baldwin DS, et al. *Eur Neuropsychopharmacol.* 2012;22:482-491; 11. Henigsberg N, et al. *J Clin Psychiatry.* 2012;73:953-959; 12. Boulenger JP, et al. *Int Clin Psychopharmacol.* 2014;29:138-149; 13. Bidzan L, et al. *Eur Neuropsychopharmacol.* 2012;22:847-857.

Patient population

AIM

PATIENTS

DESIGN

OBJECTIVES & ASSESSMENTS

Patient population

- Primary diagnosis of single or recurrent MDD
- Current MDE for <12-month duration
- Partial response (insufficient / unsatisfactory response) to SSRI / SNRI (monotherapy for ≥6 weeks at an adequate dose for current MDE)
- MADRS total score >21 and <29 (ie moderate to severe level of depression) at baseline
- ODQ[a] total score ≥50 (ie impairment in emotional functioning) at baseline
- Patient answers "Yes" to screening question on emotional effects
  - Emotional effects vary but may include, for example, feeling emotionally **"numbed"** or **"blunted"** in some way; **lacking positive emotions or negative emotions**; feeling **detached from the world around you**; or **"just not caring"** about things that you used to care about. Have you experienced such emotional effects during the last 6 weeks?

[a]ODQ is a 26-item, patient-centred, self-reported measure of emotional symptoms present in patients treated with antidepressants

MDD, major depressive disorder; MDE, major depressive episode; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–noradrenaline reuptake inhibitor; MADRS, Montgomery-Åsberg Depression Rating Scale; ODQ, Oxford Depression Questionnaire

Fagiolini A et al. Poster P.332 presented at ECNP 2020

Study design

AIM

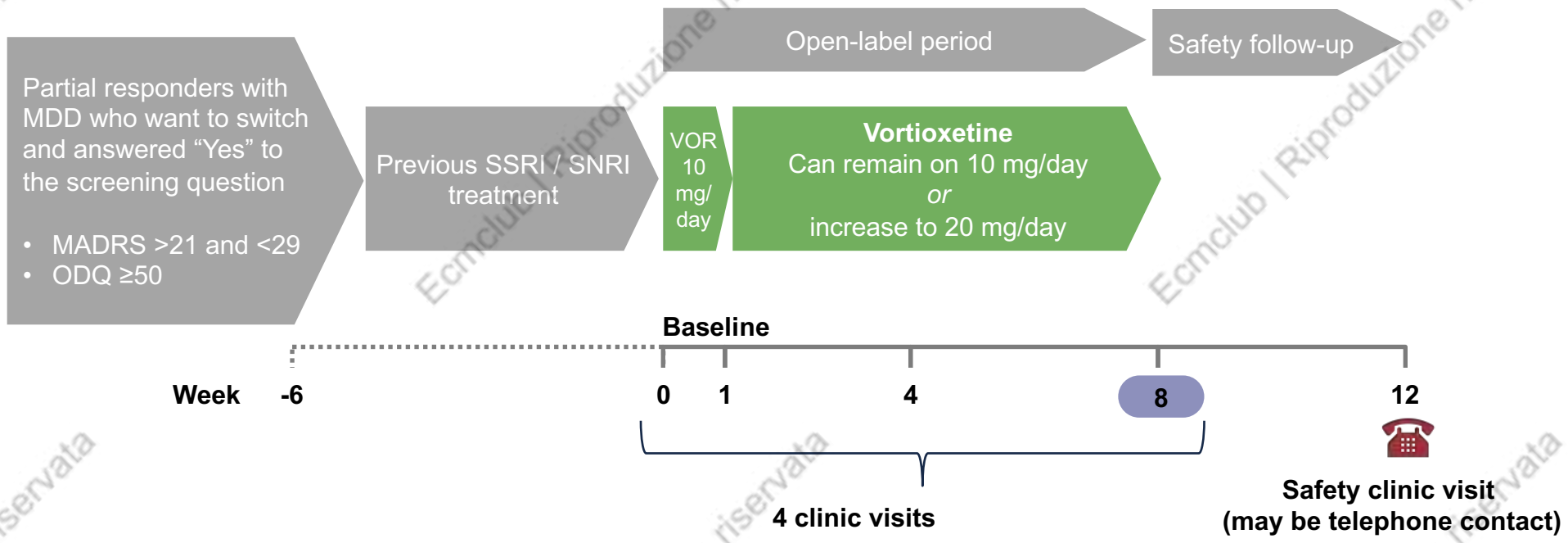
PATIENTS

DESIGN

OBJECTIVES & ASSESSMENTS

Interventional, open-label, flexible-dose, 8-week study of vortioxetine on emotional functioning in patients with MDD with partial response to SSRI / SNRI treatment

Study design



MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–noradrenaline reuptake inhibitor; MADRS, Montgomery-Åsberg Depression Rating Scale; ODQ, Oxford Depression Questionnaire

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Primary objective: ODQ

AIM

PATIENTS

DESIGN

OBJECTIVES & ASSESSMENTS

Primary objective

To assess the effectiveness of vortioxetine 10–20 mg/day on

- Emotional blunting[1]

Assessment

Emotional blunting (ODQ total score)[1]

ODQ[2]

This test is a 26-item, patient-centred, self-reported measure of emotional blunting, covering 5 dimensions:

- General reduction
- Positive reduction
- Emotional detachment
- Not caring
- Antidepressant as cause

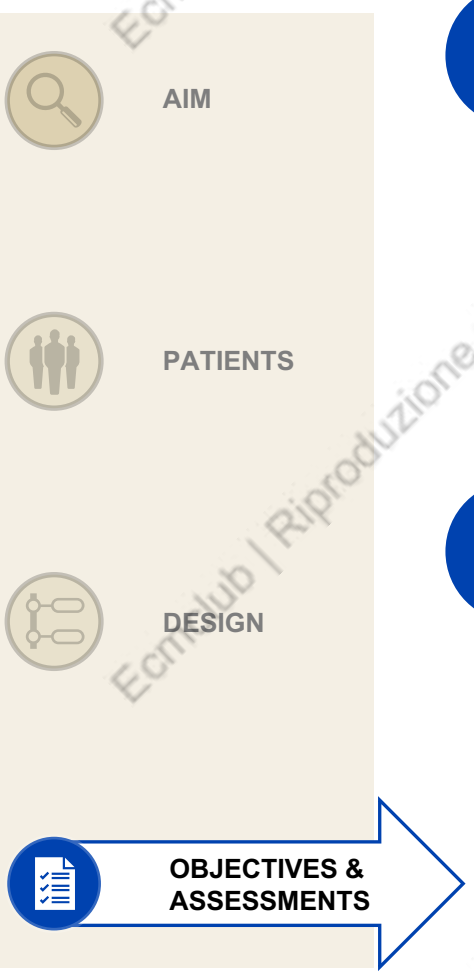
Responses are scored on a 5-point Likert scale, with a score applied to each response

Higher scores indicate a higher severity in symptoms and improvements are measured as decrease in score from baseline

ODQ, Oxford Depression Questionnaire

1. Fagiolini A et al. Poster P.332 presented at ECNP 2020;
2. Goodwin GM et al. J Affect Disord 2017;221:31-5

Secondary and safety objectives



Secondary objectives

- Motivation and energy
- Family, social and work functioning
- Cognitive functioning
- Depressive symptoms

Assessment

Change from baseline to Week 8 in

- Motivation / energy (MEI)
- Overall functioning (SDS)
- Cognitive performance (DSST)
- Depressive symptoms (MADRS, CGI-S, CGI-I)

Safety objectives

- Safety and tolerability
- Potential discontinuation symptoms following abrupt discontinuation of SSRI / SNRI and initiation of vortioxetine

Assessment

- AEs
- Discontinuation-Emergent Signs and Symptoms

MEI, Motivation and Energy Inventory; SDS, Sheehan Disability Scale; DSST, Digit Symbol Substitution Test; MADRS, Montgomery-Åsberg Depression Rating Scale; CGI-S, Clinical Global Impression - Severity; CGI-I, Clinical Global Impression - Improvement; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–noradrenaline reuptake inhibitor; AE, adverse event

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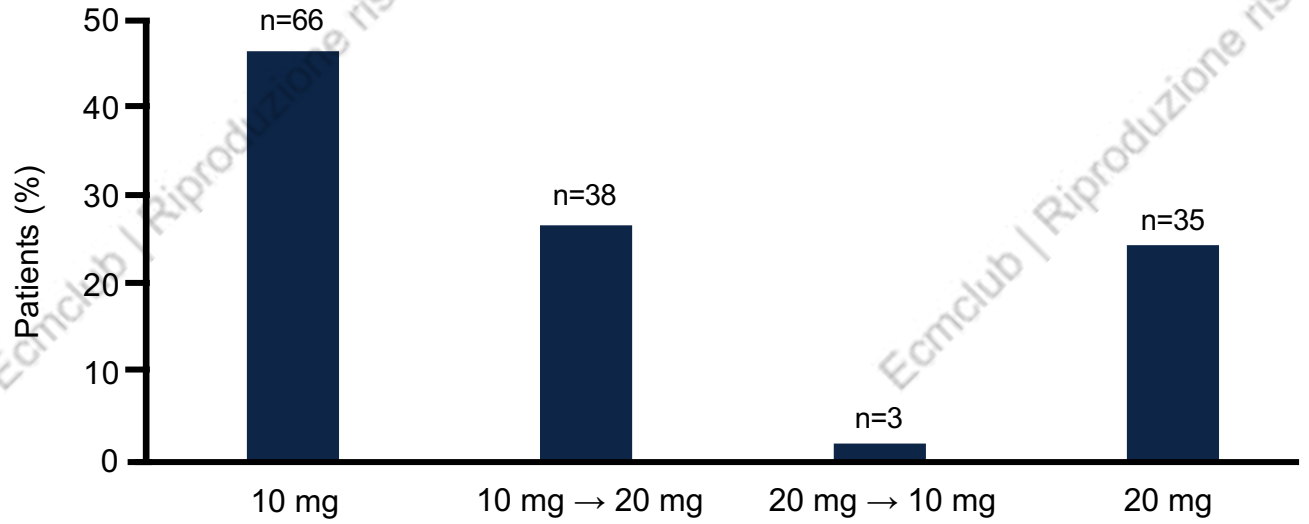
Demographics and dosing

Demographics (APTS)[1,2]	Treatment Vortioxetine (n=150)
Sex, n (%)	
Female	105 (70.0)
Male	45 (30.0)
Age	
Mean (SD)	47.1 (12.02)
Median (range)	49.5 (19–65)
Country, n (%)	
Spain	67 (44.7)
France	49 (32.7)
Lithuania	20 (13.3)
Italy	14 (9.3)
Previous treatment, n (%)	
Escitalopram	63 (42.0)
Paroxetine	26 (17.3)
Sertraline	21 (14.0)
Venlafaxine	17 (11.3)
Citalopram	13 (8.7)
Duloxetine	10 (6.7)

APTS, all patients treated set; SD, standard deviation

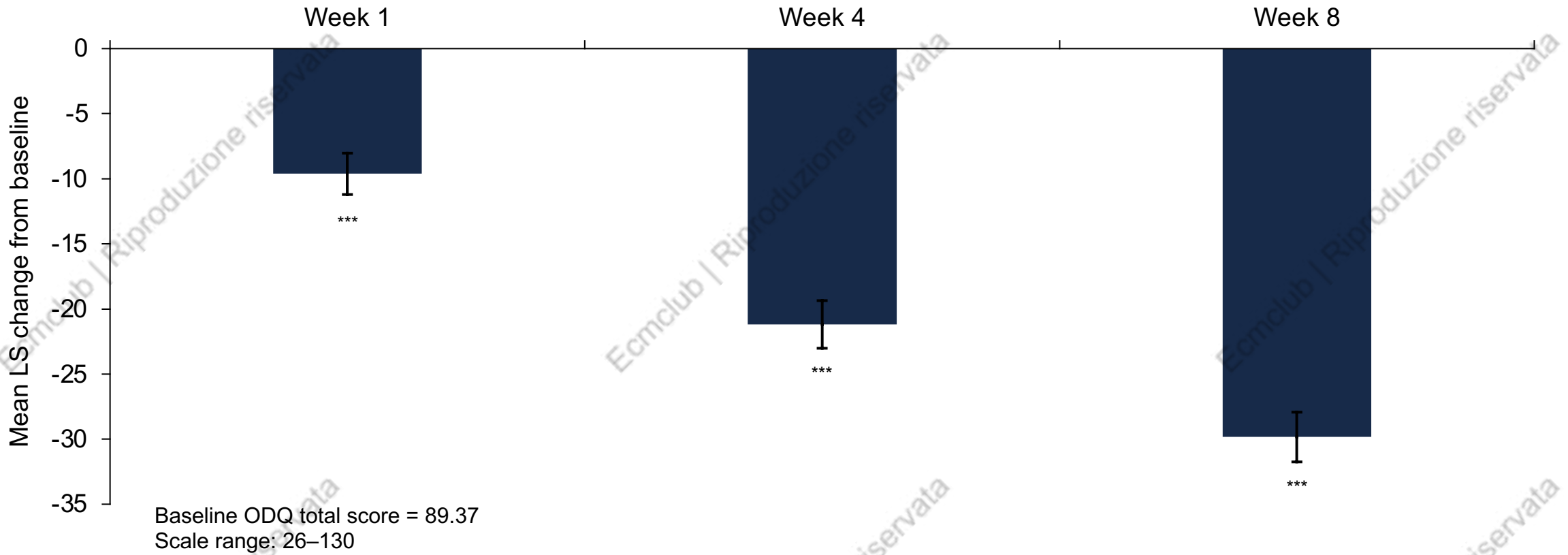
Patients grouped by sequence of vortioxetine doses taken (APTS)[2]



1. Fagiolini A et al. Poster P.332 presented at ECNP 2020;
2. Data on file

Primary end point: significant improvements in emotional blunting, as measured by the ODQ, in patients treated with vortioxetine

Change from baseline in ODQ total score (FAS, MMRM)



***Nominal p<0.0001
ODQ, Oxford Depression Questionnaire; FAS, full analysis set;
MMRM, mixed model for repeated measurements; LS, least square

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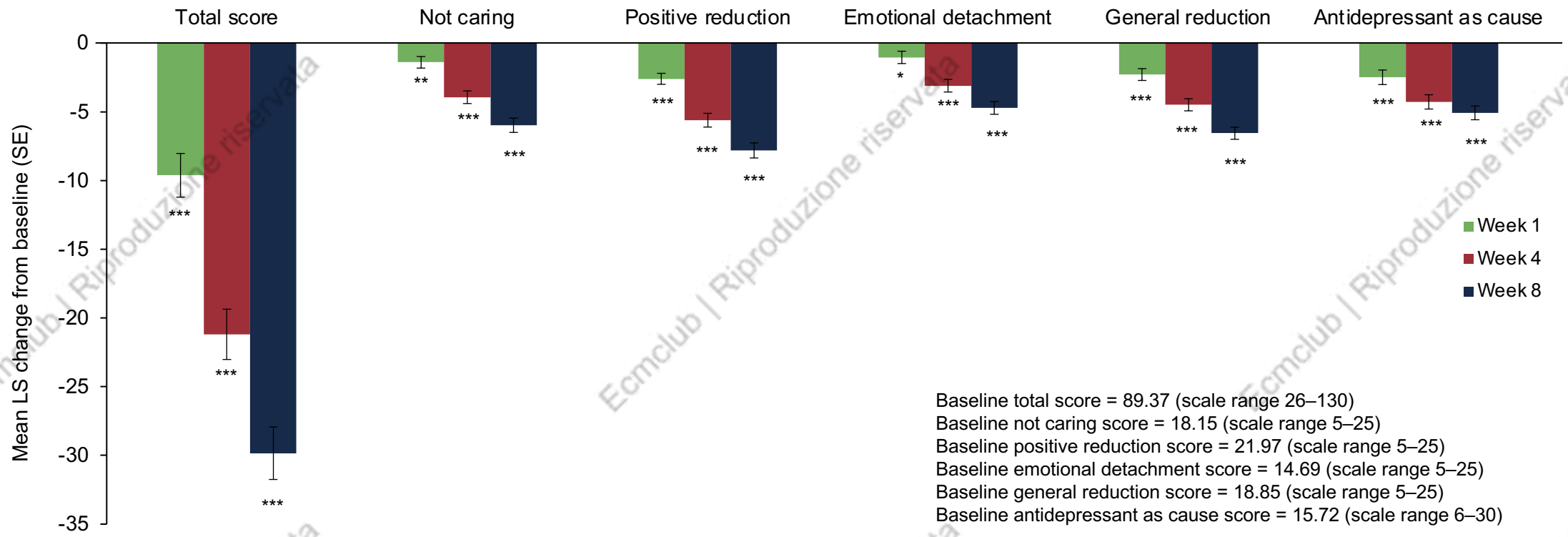
Secondary end points: broad effect on emotional blunting (significant improvement on ODQ individual domain scores) in patients treated with vortioxetine

Change from baseline in ODQ domain scores (FAS, MMRM)



Baseline total score = 89.37 (scale range 26–130)
Baseline not caring score = 18.15 (scale range 5–25)
Baseline positive reduction score = 21.97 (scale range 5–25)
Baseline emotional detachment score = 14.69 (scale range 5–25)
Baseline general reduction score = 18.85 (scale range 5–25)
Baseline antidepressant as cause score = 15.72 (scale range 6–30)

50.0% of 132 patients answered "No" to screening question on emotional effects after 8 weeks of treatment[a]

[a]138 patients answered the question after baseline (49.3% answered "No") and 132 patients answered the question >42 days after baseline
***Nominal p<0.0001; **nominal p≤0.001; *nominal p<0.05
ODQ, Oxford Depression Questionnaire; FAS, full analysis set; MMRM, mixed model for repeated measurements; LS, least square; SE, standard error

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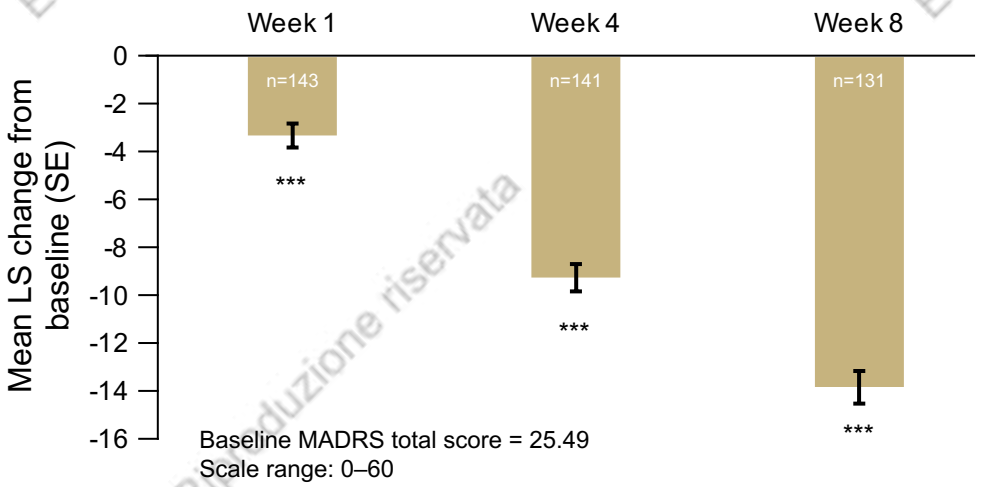
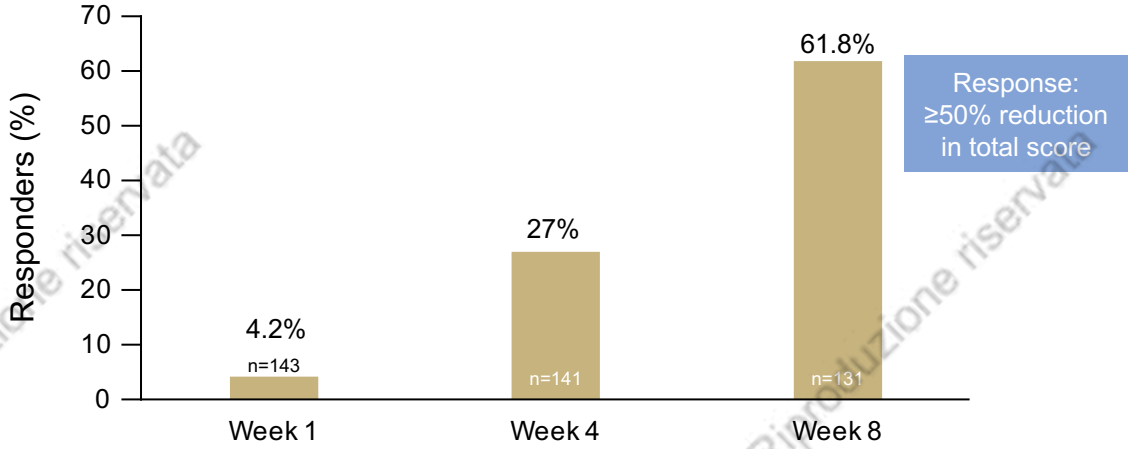
Secondary end points: significant improvement in depresssive symptoms in patients treated with vortioxetine

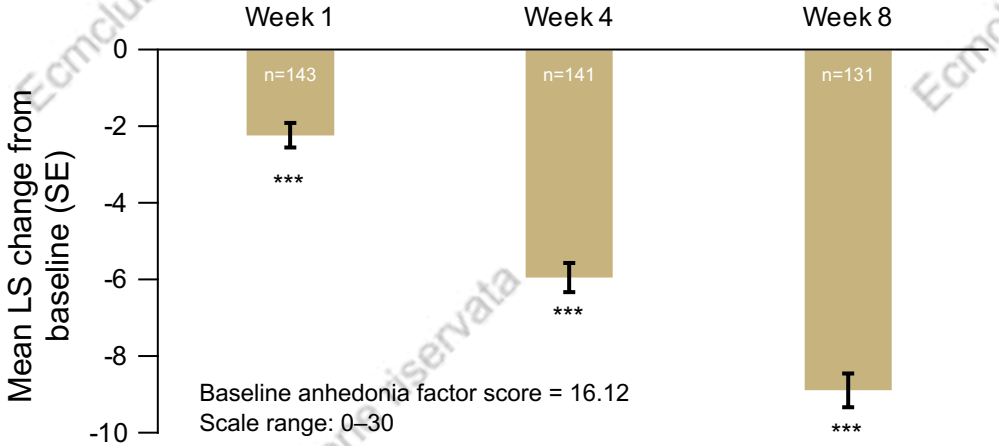
Change from baseline in MADRS total score (FAS, MMRM)[1]



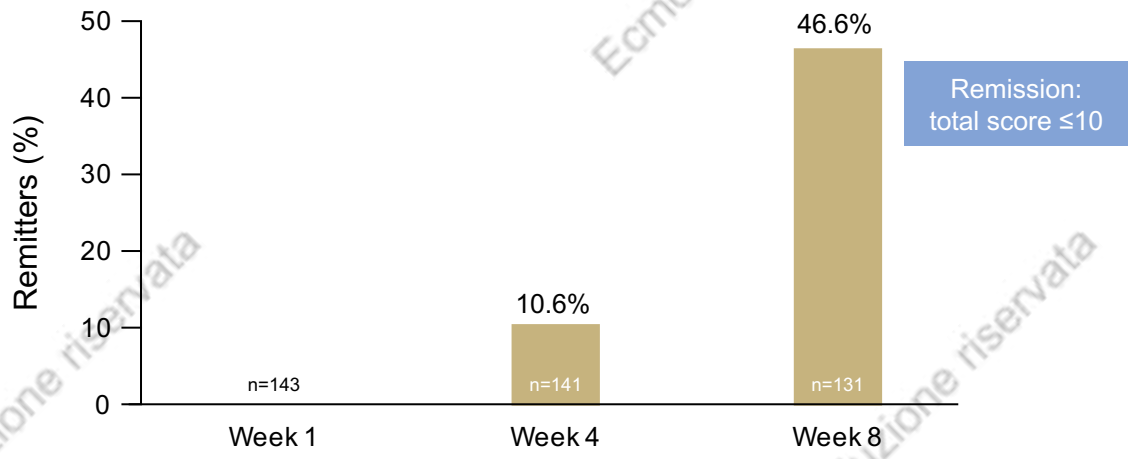
Response in MADRS total score (FAS, OC)[2]



Change from baseline in MADRS anhedonia factor score (FAS, MMRM)[2]



Remission in MADRS total score (FAS, OC)[2]



***Nominal p<0.0001
MADRS, Montgomery-Åsberg Depression Rating Scale; FAS, full analysis set;
MMRM, mixed model for repeated measurements; LS, least square; SE, standard error; OC, observed cases

1. Fagiolini A et al. Poster P.332 presented at ECNP 2020; 2. Data on file

AEs: TEAEs

Open-label treatment period: TEAEs by preferred term (APTS)[1]	
Preferred term	**Vortioxetine (n=150)**
Patient exposure, years	21
Patients with TEAEs, n (%)	71 (47.3)
Nausea	31 (20.7)
Headache	12 (8.0)
Dizziness	10 (6.7)
Vomiting	10 (6.7)
Diarrhoea	9 (6.0)
Nightmare	6 (4.0)
Abdominal distension	5 (3.3)
Pruritus	5 (3.3)
Abnormal dreams	4 (2.7)
Pruritus generalised	4 (2.7)

Open-label treatment period: TEAEs leading to withdrawal by preferred term (APTS)[2]	
Preferred term	**Vortioxetine (n=150)**
Patient exposure, years	21
Patients with TEAEs, n (%)	6 (4.0)
Vomiting	4 (2.7)
Nausea	3 (2.0)
Diarrhoea	2 (1.3)
Abdominal pain upper	1 (0.7)
Chromaturia	1 (0.7)
Dizziness	1 (0.7)
Feeling abnormal	1 (0.7)
Nightmare	1 (0.7)

AE, adverse event; TEAE, treatment-emergent adverse event; APTS, all patients treated set

1. Fagiolini A et al. Poster P.332 presented at ECNP 2020; 2. Data on file

Conclusions

- About 50% of patients have a partial response to SSRI and do not reach full functional recovery
- The **burden** of blunting can lead to **treatment discontinuation**, an increased risk of **relapse** and **prevent full functional recovery** in patients with MDD[2-4]
- In patients with MDD treated with an SSRI or SNRI who only have a partial response and suffer from emotional blunting, **50% report absence** of emotional blunting after **8 weeks** of treatment with **vortioxetine 10 or 20 mg**
- The **ultimate goal** of treating MDD is to achieve **full functional recovery**; **tolerable** and **effective** treatments are essential to **promote adherence**

MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–noradrenaline reuptake inhibitor

1. Rush AJ, et al. Am J Psychiatry. 2006;163:1905–17;; 2. Goodwin GM et al. J Affect Disord 2017;221:31-5; ; 3.
2. Sirey JA et al. JAMA Psychiatry 2017;74:1129-35; 4. Rosenblat JD et al. J Affect Disord 2019;243:116-20