

Clinical experience learned from approved esketamine and potential implications for psychedelics

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Disclosures: Professor Philip Gorwood

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Grants	none
Honoraria	Biogen, Janssen, Lundbeck, Merk, Otsuka, Richter and Viatriis
Shares	none
Paid positions	none
Lectures and advisory boards	Janssen, Lundbeck, Otsuka and Viatriis
Consultant	none
Other involvement	none

There is a significant burden of Treatment Resistant Depression (TRD)



Higher **severity**
(+2, HRDS)



Higher **Suicidal**
Ideas (x3)



Impaired **QoL**
(-6, SF-12)



Higher **absenteeism**
(RR=x1.5)



More **hospitalisation**
(OR=x1.8)



More **ER frequency**
(OR=x1.5)

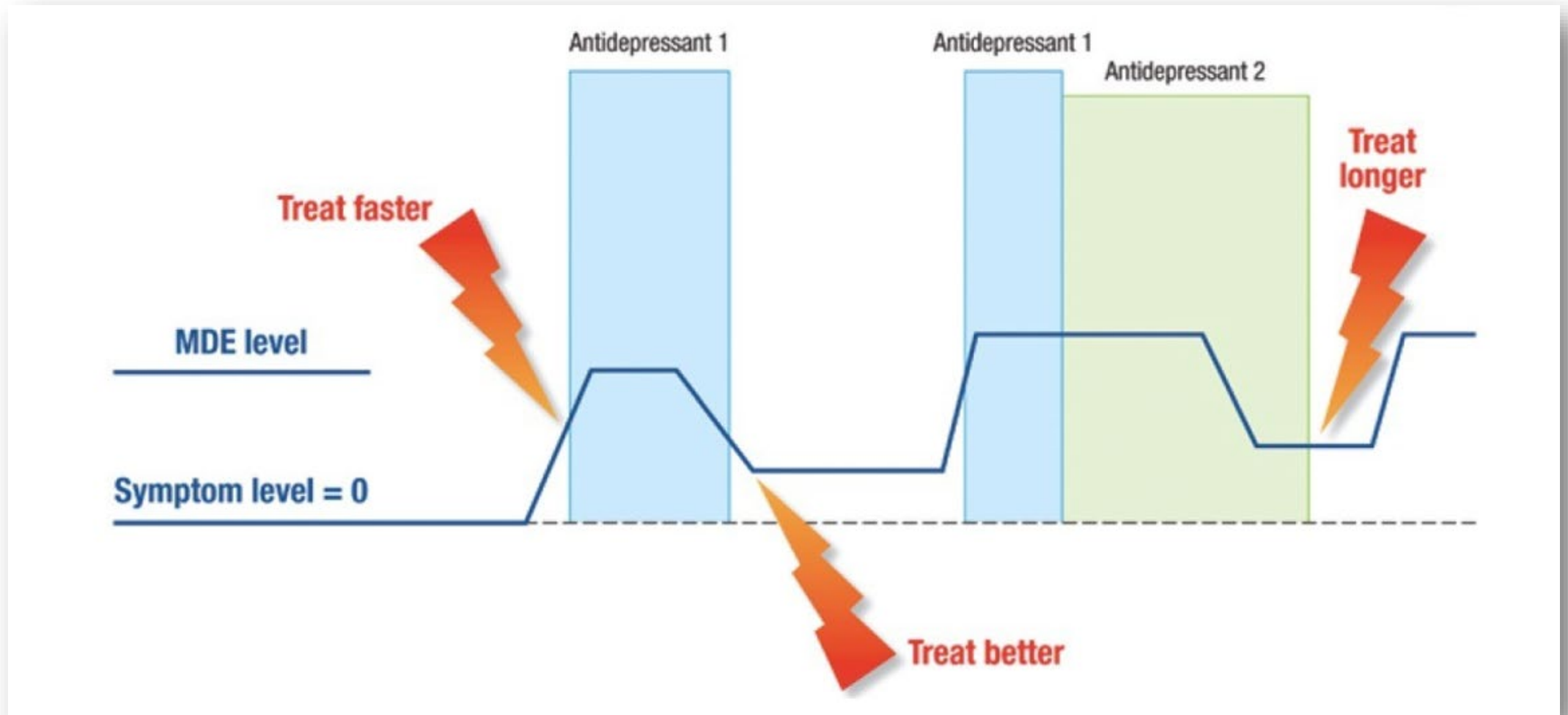


More **comorbidities**
(+6% with >3)



Higher **costs**
(+1.5k€/year)

Research on MDE treatment¹



Options for the management of TRD

<u>Option</u>	<u>Rational</u>
Extend current treatment	Late responders
Switch	Other MoA
Combine	Target specific symptoms Build on what was obtained
Ketamine	Rapid onset
Esketamine	Rapid onset & > SGA
SGA	Easy
ECT	Gold standard
rTMS	High acceptance
Vague nerve stimulation	Chronicity
Psychotherapies	At all stages

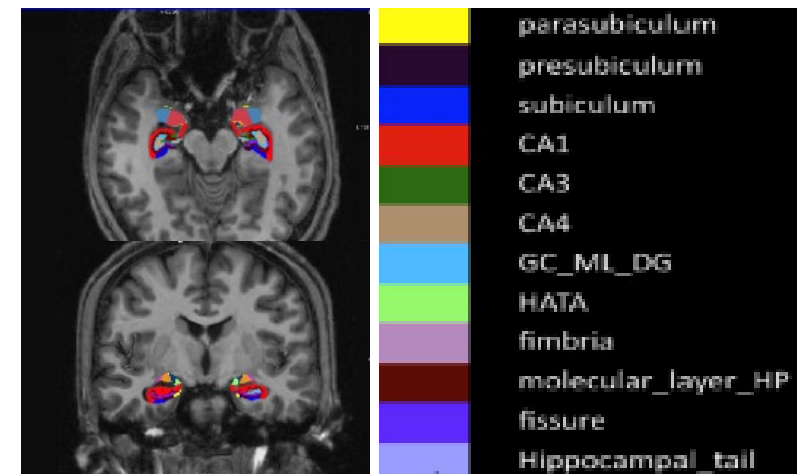
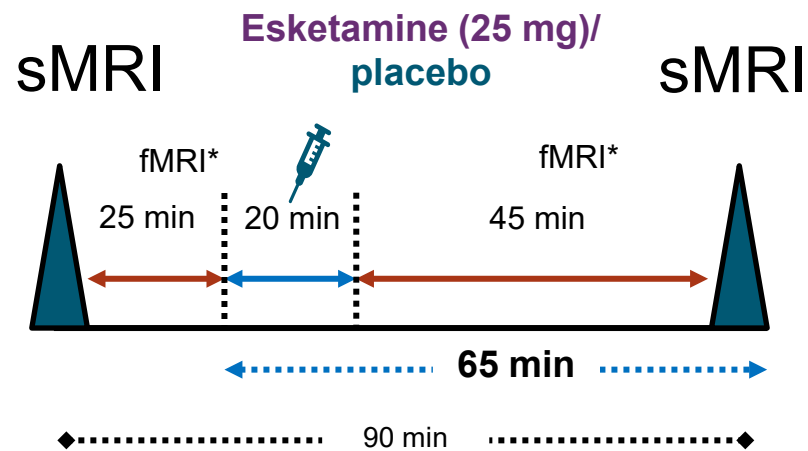
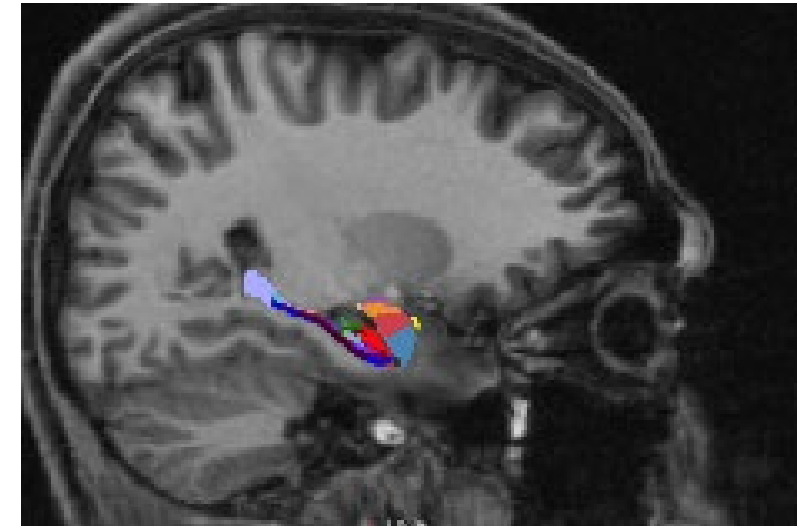
Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions

Roger S. McIntyre¹⁻³, Mohammad Alsuwaidan³, Bernhard T. Baune^{4,5}, Michael Berk^{5,6}, Koen Demyttenaere⁷, Joseph F. Goldberg⁸, Philip Gorwood⁹, Roger Ho^{10,11}, Siegfried Kasper¹², Sidney H. Kennedy³, Josefina Ly-Uson¹³, Rodrigo B. Mansur³, R. Hamish McAllister-Williams¹⁴, James W. Murrough⁸, Charles B. Nemeroff¹⁵, Andrew A. Nierenberg¹⁶, Joshua D. Rosenblatt³, Gerard Sanacora¹⁷, Alan F. Schatzberg¹⁸, Richard Shelton¹⁹, Stephen M. Stahl²⁰, Madhukar H. Trivedi²¹, Eduard Vieta²², Maj Vinberg²³, Nolan Williams¹⁸, Allan H. Young²⁴, Mario Maj²⁵

(*World Psychiatry* 2023;22:394–412)

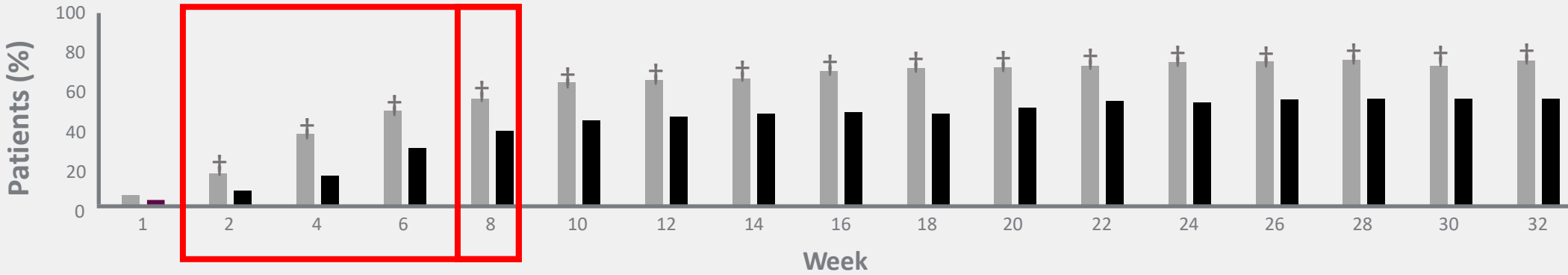
Volume increase of the hippocampus after 65 min of esketamine (vs placebo)

- Patients with MDD¹ have **decreased hippocampal volume**
- Ketamine **rescue spine formation** after 24h in rats²
- Esketamine infusion **increased hippocampal volume** in healthy controls **in one hour**, showing rapid neuroplastic effects³



Treatment response* with SPRAVATO[®] + SSRI/SNRI vs quetiapine XR + SSRI/SNRI at any time point¹

Response rates over time (LOCF)

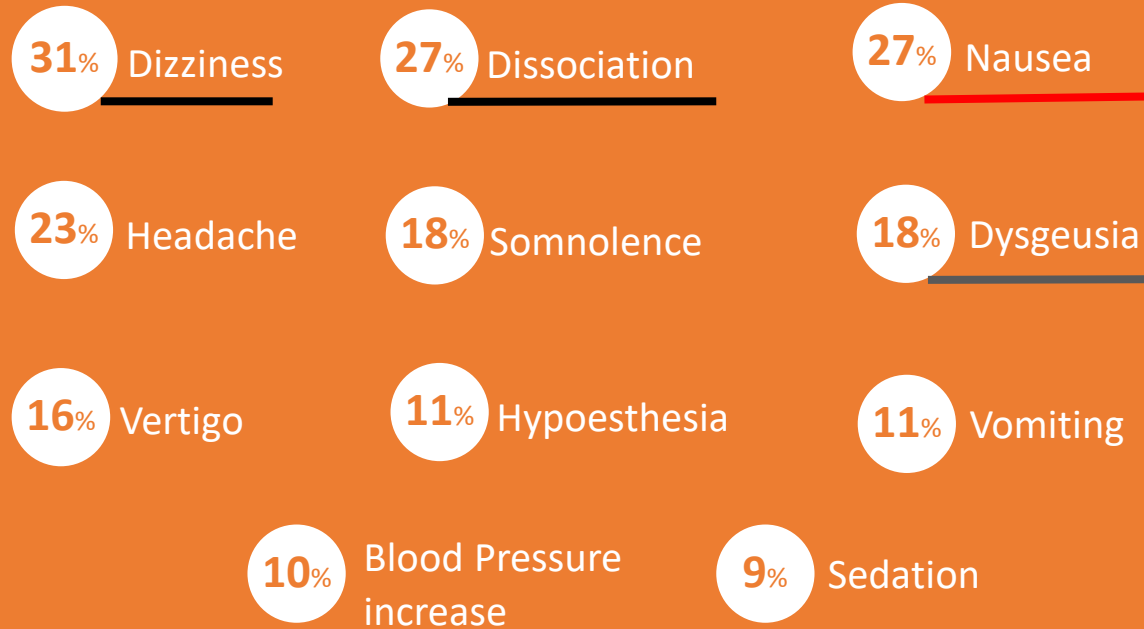


SPRAVATO [®] + SSRI/SNRI (n=325):	327	327	327	327	327	327	327	327	327	327	327	327	327	327	327	327
Quetiapine XR + SSRI/SNRI (n=326):	330	330	330	330	330	330	330	330	330	330	330	330	330	330	330	330

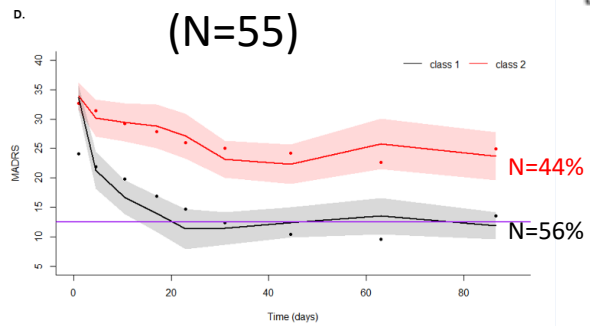
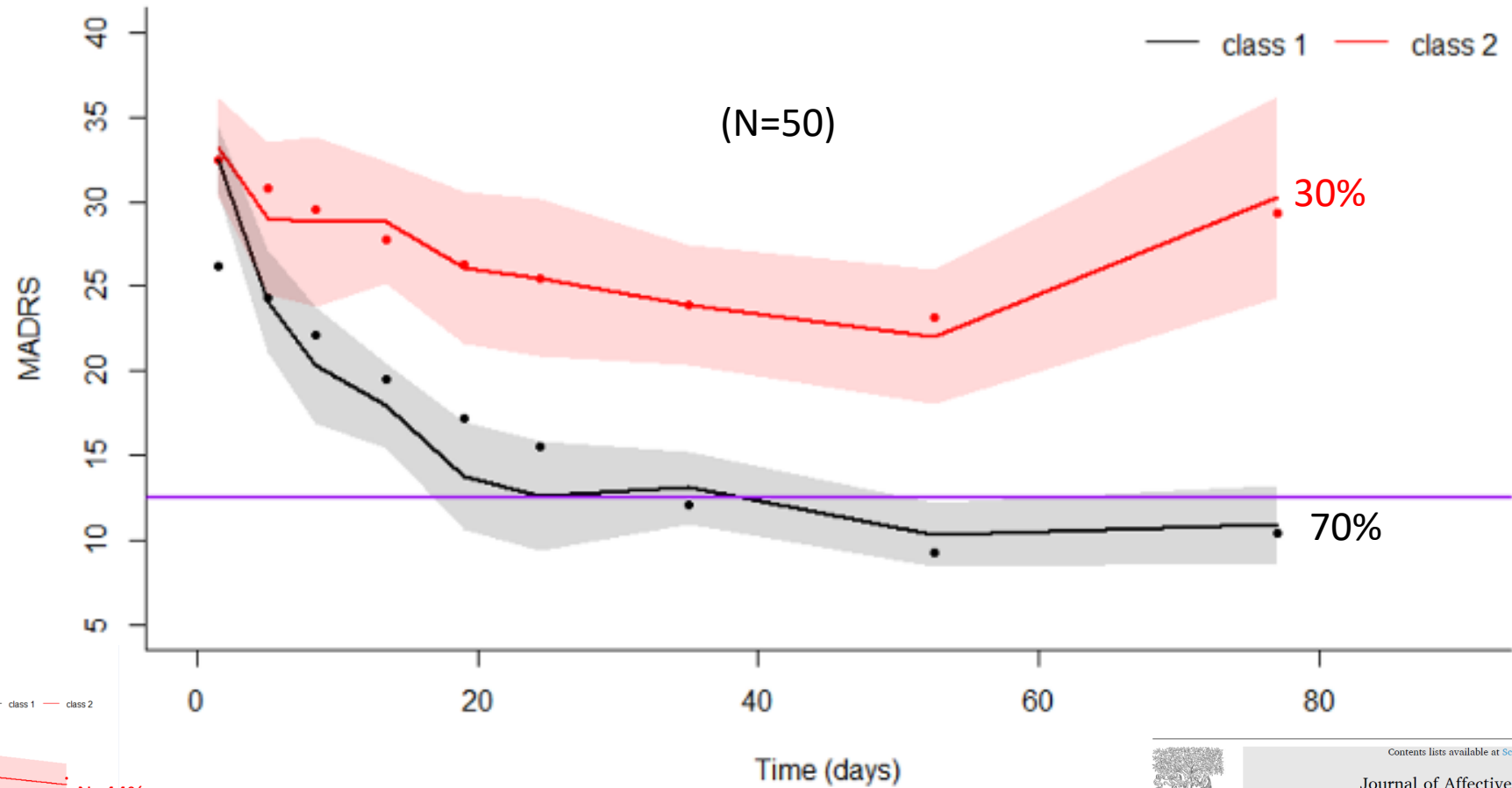
SPRAVATO[®] + SSRI/SNRI (n=336)
 Quetiapine XR + SSRI/SNRI (n=340)

Esketamine tolerability

Most commonly observed Adverse Events



Two trajectories of treatment response in TRD



When should we take a decision ?

Day (100)	AUC	PPV	NPD	Accuracy	OR
First visit	0.549				
Day 3	0.768	86.8%	61.5%	74.3%	10.5
Day 7	0.845	90.9%	68.0%	80.0%	21.3
Day 10	0.829	92.7%	70.0%	81.9%	29.7
Day 14	0.886	90.0%	73.3%	82.9%	24.8



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Research paper

Early effects predict trajectories of response to esketamine in treatment-resistant depression

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 Rebecca Perrain^g, Fabien Vinckier^{b,c,g}, Lila Mekaoui^h, Raphaël Gaillard^{b,c},
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Conclusions

- New *mechanism* (immediate effect), new delivery *organisation* (atypical settings with pros and cons), new *monitoring* (quick efficacy and side-effects, unclear long term effects), new *costs* (therefore accessibility), new *risks* (but no abuse)... creating new hopes and requests for patients
- Treatment given in centers and with shorter delay of action are resolving one of the main problem: *compliance* !
- But also many lessons learned
 - The need/benefit of specific setting (staff, room & *human* decoration, *medical* monitoring)
 - We can (should?) use largely & quickly... and quickly drop it if poor response
 - TRD are not being correctly treated (for >50% : 5 years disorder, 4 episodes, single treatment, single clinician)

Thank you!

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