UNIVERSITÀ DEGLI STUDI
DI GENOVA

XXI Congresso Nazionale Società Italiana di NeuroPsicoFarmacologia. Elementi innovativi in NeuroPsico Farmacologia e nuove frontiere terapeutiche

«Agonisti parziali della dopamina e trattamento dimensionale delle depressioni»

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DINOGMI 2018-2022 | DIPARTIMENTO DI ECCELLENZA MIUR

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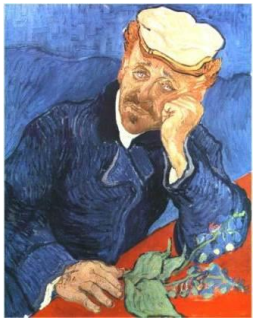
Corso Magenta, 61 - Milano

What are the main reasons for the dimentional treatment of major depression?



Vincent van Gogh

Unmet needs (e.g., 1) delayed mechanism of action, 2) adverse effects, 3) residual symptoms, 4) lower remission rates, 5) persistent cognitive impairment)

……Nearly **30% of MDD patients have failed response to antidepressants** or psychotherapy and are referred to as having **treatment resistant depression**

Compared with other **patients**, those **with unmet needs and TRD** have **lower productivity**, **higher medical comorbidity**, and **more suicidality**

To improve remission rates, **it is important to explore alternative therapeutic strategies**

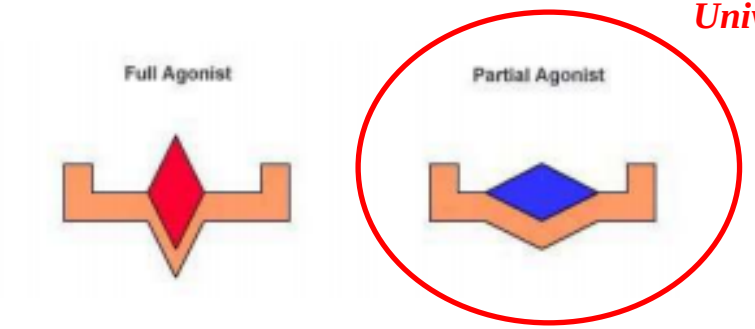
Rush et al. Acute Am J Psychiatry. 2006;163(11):1905-1917; Trevino et al., Ann Clin Psychiatry. 2014;26(3):222-232; Amital et al., J Affect Disord. 2008; 110(3):260-264

Dopamine partial agonists: history and background

Judy Hope Monash University, Australia

For about a decade **during the 1990s, studies** with partial dopamine agonists **could not demonstrate efficacy**

The **probable reason** was that **the drugs tested did not have the appropriate agonist:antagonist ratios.**



The <u>full agonist</u> is able to induce a conformational R change leading to a maximal effect (a measure of the intrinsic activity)

<u>Partial agonists</u> are able to **induce some degree of R activation** but **not of sufficient magnitude for** a **maximal response (intrinsic activity between 0 and 1)**

Hope et al., Austral Psychiatry, 2018

The strategy of targeting D1- and D2-like receptors

D1-like receptors → **coupled to Gαs/olf** → **increase cAMP** → **increase PKA activity**

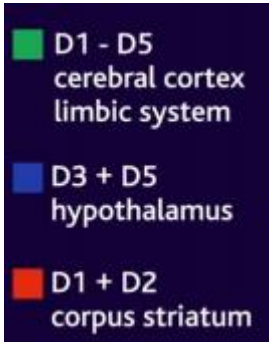
D2-like receptors → **coupled to Gαi/o** → **reduce cAMP** → **reduce PKA activity**

D1Rs → **regulate BDNF** expression **in hippocampus/PFC** (the major post-synaptic receptor subtype) → **spatial working learning**; **memory processes**


Paul Greengard

D3Rs → **movement**; **cognition** → **neurodegenerative diseases**; **emotion**; **memory**; **reward and addiction**


Pierre Sokoloff



D4R → **increased LTP in Schaffer collateral-CA1** of aged mice → **cognitive decline in aging**

D1Rs and D5Rs → **control growth, differentiation,** hippocampal LTP and **memory**

Xing et al., Behav. Brain Res. 2012; Sarinana, et al., Proc. Natl. Acad. Sci. U. S. A. 2014; Yang et al., Ageing Res Rev 2020

REVIEW ARTICLE

CNS Drugs 2004; 18 (4): 251-267
1172-7047/04/0004-0251/$31.00/0

Dopamine Partial Agonists

A New Class of Antipsychotic

Jeffrey A. Lieberman

University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA

Jeffrey A. Lieberman

Abstract

This review examines the development of dopamine partial agonists as a new class of antipsychotic agents. Partial agonists have a lower intrinsic activity at receptors than full agonists, allowing them to act either as a functional agonist or a functional antagonist, depending on the surrounding levels of naturally occurring neurotransmitter (full agonist). In the absence of a full agonist, partial agonists show functional agonist activity, binding to the receptor to produce a response. In the presence of a full agonist, partial agonists show functional antagonist activity, as receptor binding reduces the response from that seen with the full agonist. A partial agonist at dopamine D_2 receptors therefore offers an attractive option for the treatment of schizophrenia. It should act as a functional antagonist in the mesolimbic dopamine pathway, where excessive dopamine activity is thought to cause positive symptoms, but show functional agonist activity in the mesocortical pathway, where reduced dopamine activity is thought to be associated with negative symptoms and cognitive impairment. In addition, it should avoid the

Lieberman JA. Dopamine partial agonists: a new class of antipsychotic. CNS Drugs 2004; 18: 251-267

CNS Spectrums (2017), **22**, 375–384.
doi:10.1017/S1092852917000608

BRAINSTORMS—Clinical Neuroscience Update

Drugs for psychosis and mood: unique actions at D3, D2, and D1 dopamine receptor subtypes

Stephen M. Stahl

Stephen Stahl

ISSUE:

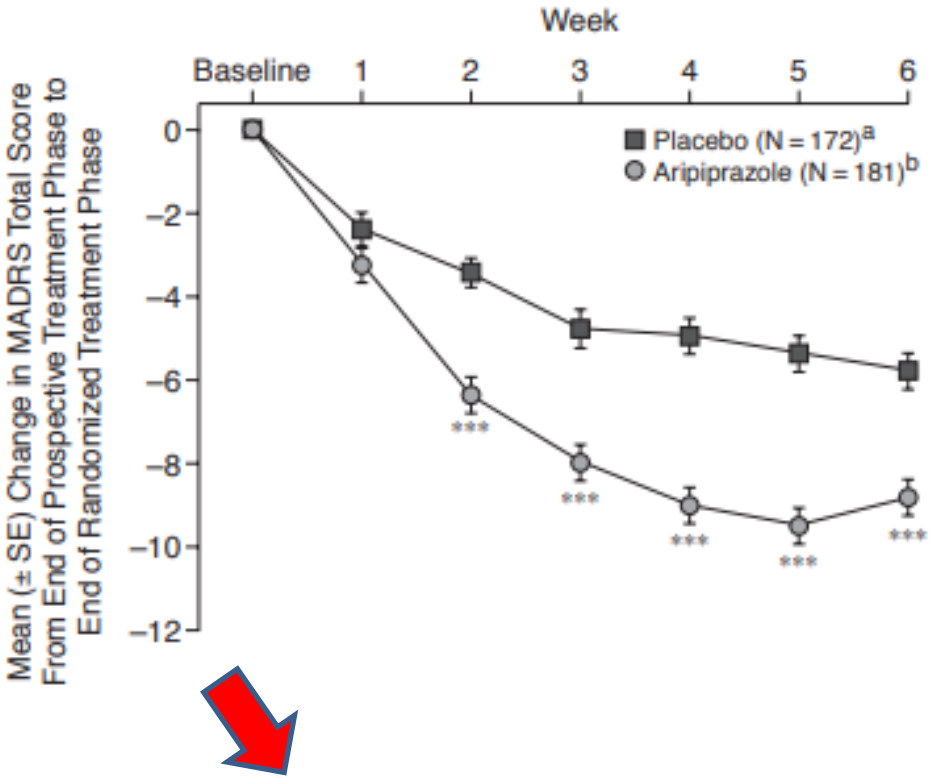
Drugs for psychosis and mood that bind dopamine D2 receptors can be classified not only by whether they also block serotonin 2A receptors, but by whether they also bind D3 or D1 receptors.

A new classification of drugs binding D2R creates 3 different categories: **those preferentially binding D2 receptors** (most of these agents), **those** also **binding D3 receptors effectively** (cariprazine>blonanserin), and **those that also bind D1 receptors** (asenapine, clozapine, and olanzapine> quetiapine and ziprasidone)

These 3 classes theoretically **have potential clinical implications**, such as **improvement in cognition**, **motivation**, and **mood**

Ki (nM)	D3	D2	D1
Dopamine (DA)	60	540	1766
D2 BINDING ONLY			
Brexpiprazole*	1.1	0.3	164
Paliperidone	2.6	1.4	41
Aripiprazole	4.6	2.3	1173
Risperidone	7.3	3.7	327
Ziprasidone	7.3	4.75	80
Iloperidone	10.5	8.3	129
Lurasidone**	15.7	0.66	262
Quetiapine	394	437	1096
D2 + D1 BINDING			
Asenapine	1.8	1.7	2.9
Olanzapine	38.05	30.75	56.6
Clozapine	310	147	240
D2 + D3 BINDING			
Cariprazine***	0.09	0.49	1000
Blonanserin****	0.494	0.142	1090

The efficacy/safety of aripiprazole, a first class adjunctive agent to ADs in inadequately treated MDD (approved in 2007): a multicenter, randomized, double-blind, placebo-controlled study

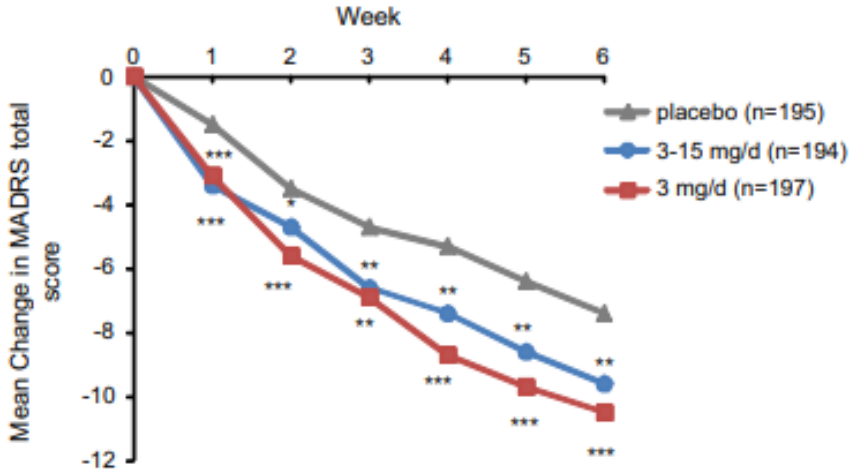


- A **total of 178 patients** were **randomly assigned to** adjunctive **placebo and 184 to** adjunctive **aripiprazole**.
- **Rapid improvements** in **MADRS** total scores **<u>as early as week 2</u>.**
- **Continuous improvement in the aripiprazole group.**

In patients with MDD who showed an incomplete response to antidepressants, adjunctive aripiprazole was efficacious and well tolerated

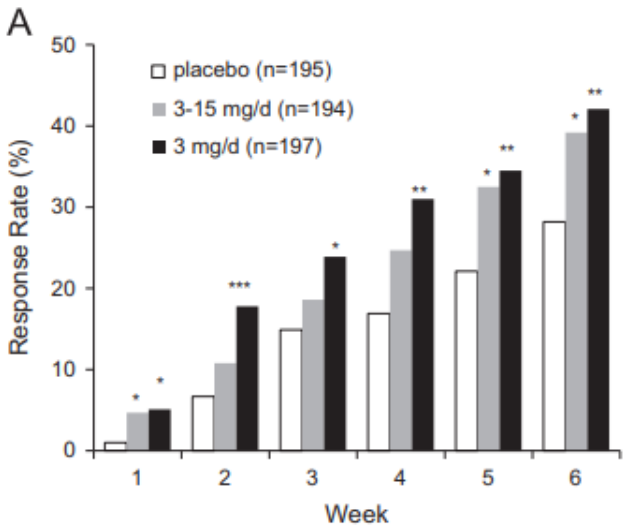
(Berman et al., J Clin Psychiatry 2007, 2009)

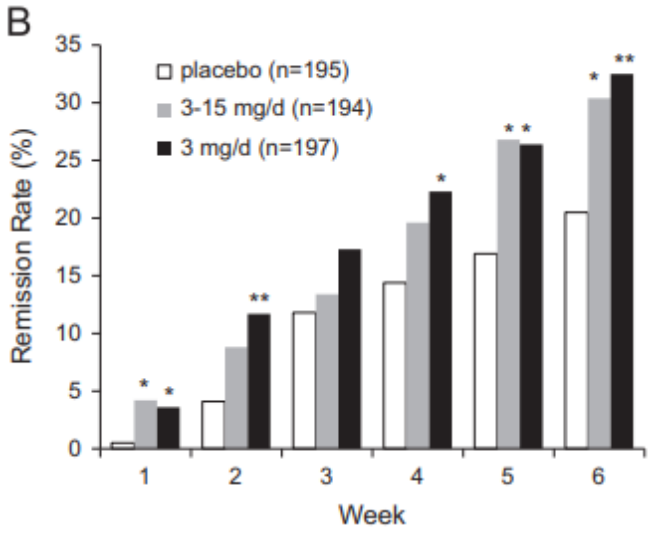
Aripiprazole as augmentation therapy was effective in Japanese patients with MDD



Adjunctive aripiprazole was significantly **superior** (with **comparable clinical benefits between** the fixed dose (**3 mg**/day) and flexible dose (**3–15 mg**/day) **to adjunctive placebo** in improving depressive symptoms at endpoint and **the onset of activity** was **evident <u>from Week 1</u>**

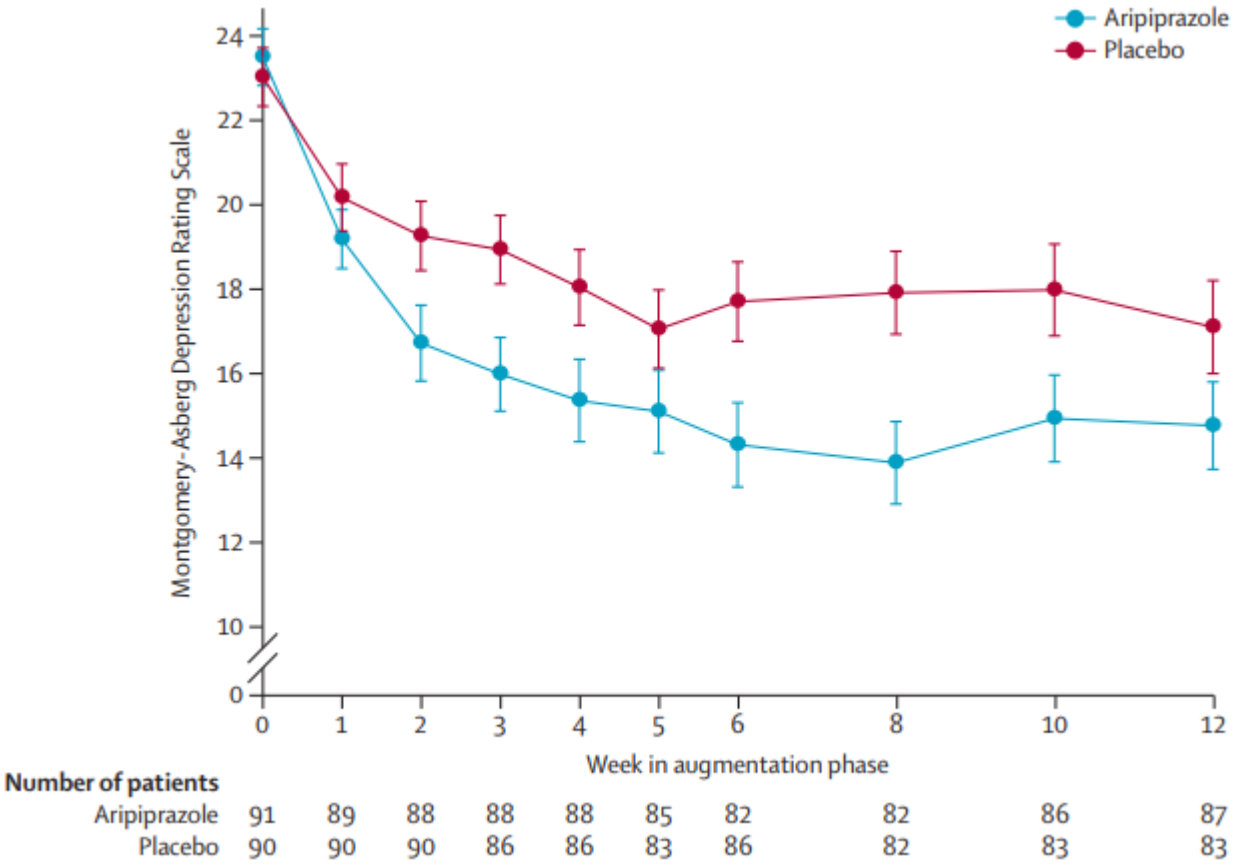
N=586





(Kamijima et al., J Affect Disord 2013)

Augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life



- **N=181** (39%) did not remit, **91** were **randomised to aripiprazole,** and **90** were **randomised to placebo**

- **Aripiprazole benefits** in this trial **included a reduction of suicidal ideation** based on Scale of Suicidal Ideation **and health-related quality of life**

In adults aged 60 years or older who do not achieve remission from depression with a first-line antidepressant, **the addition of aripiprazole is effective in achieving and sustaining remission**

(Lenze et al., Lancet 2015)

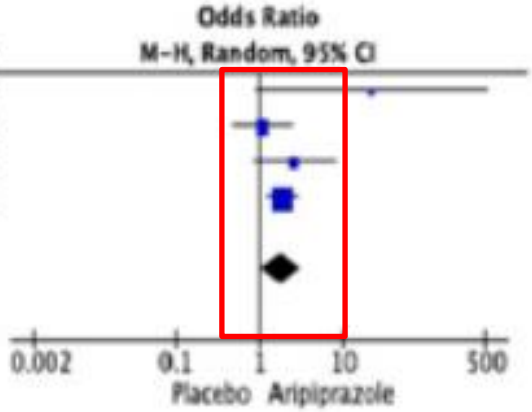
Forest plot for MDD: aripiprazole at low doses

Response

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Lin 2011	8	8	3	7	2.7%	21.86 [0.91, 523.42]	2011
Fava 2012b	10	54	29	167	28.1%	1.08 [0.49, 2.39]	2012
Fava 2012a	11	61	5	63	17.2%	2.55 [0.83, 7.84]	2012
Kamijima 2013a	83	197	55	195	52.1%	1.85 [1.22, 2.82]	2013
Total (95% CI)		**320**		**432**	**100.0%**	**1.80 [1.06, 3.04]**	
Total events	112		92				

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 4.35$, $df = 3$ ($P = 0.23$); $I^2 = 31\%$

Test for overall effect: $Z = 2.18$ ($P = 0.03$)

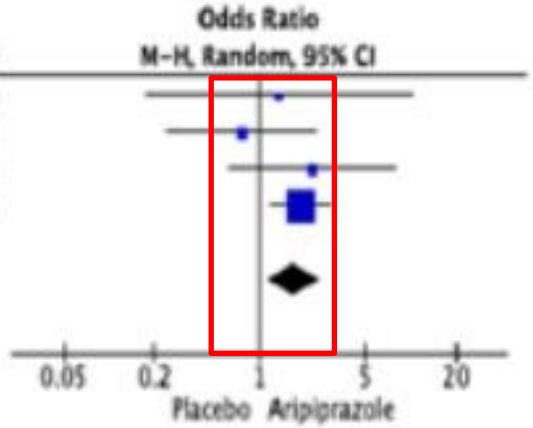


Remission

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Lin 2011	4	8	3	7	3.7%	1.33 [0.17, 10.25]	2011
Fava 2012b	4	54	16	167	12.0%	0.76 [0.24, 2.36]	2012
Fava 2012a	8	61	4	63	9.9%	2.23 [0.63, 7.82]	2012
Kamijima 2013a	64	197	40	195	74.4%	1.86 [1.18, 2.95]	2013
Total (95% CI)		**320**		**432**	**100.0%**	**1.68 [1.13, 2.50]**	
Total events	80		63				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.33$, $df = 3$ ($P = 0.51$); $I^2 = 0\%$

Test for overall effect: $Z = 2.58$ ($P = 0.010$)



Improvements of both response (OR: 1.8) and remission (OR: 1.68) rates were found **for low-dose aripiprazole as an add-on to antidepressants**

Romeo et al., J Psychopharmacol 2018

Aripiprazole as add-on treatment to standard antidepressants: heterodimers variants ore weakly coupled with trasductions proteins

The **pharmacological activity** of aripiprazole **could be** more **complex when considered** in the context of **DR heteromerization**

Certain actions of aripiprazole **may reflect: 1) low efficacy stimulation of D2R, 2) D3R or D2R/D3R receptors (antagonist)**, **3)** while **other effects may reflect blockade of D3R,** and/or **4) D2R/D3R heterodimers weakly coupled to transduction mechanisms**

Leggio et al., Pharmacol Ther 2016

For example, the observation that the partial agonist activity of aripiprazole at D2R is abrogated upon co-expression of D3R indicates that **at D2R/D3R heterodimers aripiprazole seems to behaves as D2R antagonist**.

(Novi et al., J Neurochem 2007)

However, the receptor mechanism through which aripiprazole exerts its antidepressant action remains to be precisely **defined**

(Leggio et al., Pharmacol Ther 2016)

What are the factors (other than affinity) that may influence the effects of dopamine partial agonists?

1 **Repeated** administration of **antipsychotics**

↑ **D2R** family **number in the high affinity state**
(Seeman et al., Synapse, 2005)

↑ **high affinity receptors number augments the efficacy of D2/D3R partial agonists**

2 **Changes in receptor reserve** are **relevant for partial agonists with a high affinity** for the receptors

In systems with significant **D2R/D3R reserve, partial agonists** show **90% of full agonism**
(Burris et al., J Pharmacol Exp Ther 2002; Tadori et al., Eur J Pharmacol 2009)

3 **D1-D3, D1-D2, D2-D3 heterodimers** have **different signaling properties** than monomers

4 The amount of drug binding depends on **binding affinity**, **dose of the drug,** but even **dopamine levels**

5 **Heterodimers** may be **strongly/weakly coupled to transduction mechanisms**

(Varela et al., J Psychopharmacol 2014; Gao et al., J Psychopharmacol 2015)

The second class of medications approved as adjunctive agents to antidepressants

Brexpiprazole

In **May 2017**, the **Australian Therapeutic Goods Administration approved brexpiprazole** for the treatment of schizophrenia in adults

Australian Government

Department of Health

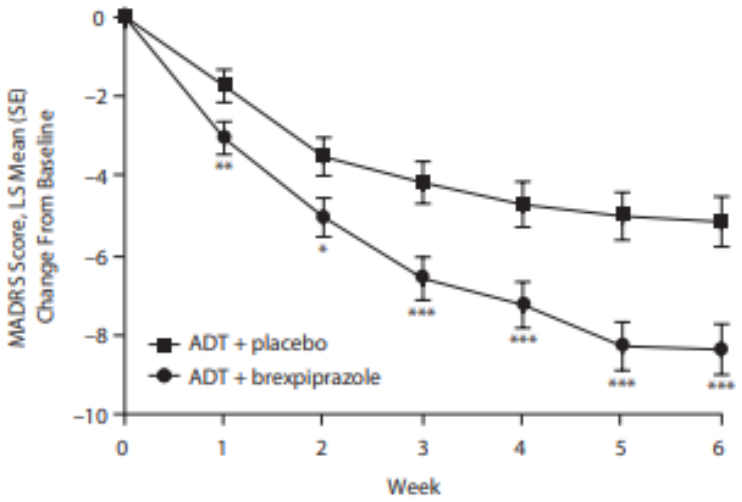
Therapeutic Goods Administration

Brexpiprazole
a **third generation AP** → **a broad receptor binding profile**

- **lower intrinsic activity at** dopamine **D2** receptor
- **higher intrinsic activity at 5-HT1A**
- **higher affinity** for **α 1b/2c adrenergic** receptors

Lundbeck Australia. REXULTI (Brexpiprazole) product information. North Ryde, 2017; Björkholm et al., Eur Neuropsychopharmacol 2017

Efficacy and Safety of Adjunctive Brexpiprazole 2 mg in Major Depressive Disorder:
A Phase 3, Randomized, Placebo-Controlled Study in Patients With Inadequate Response to Antidepressants

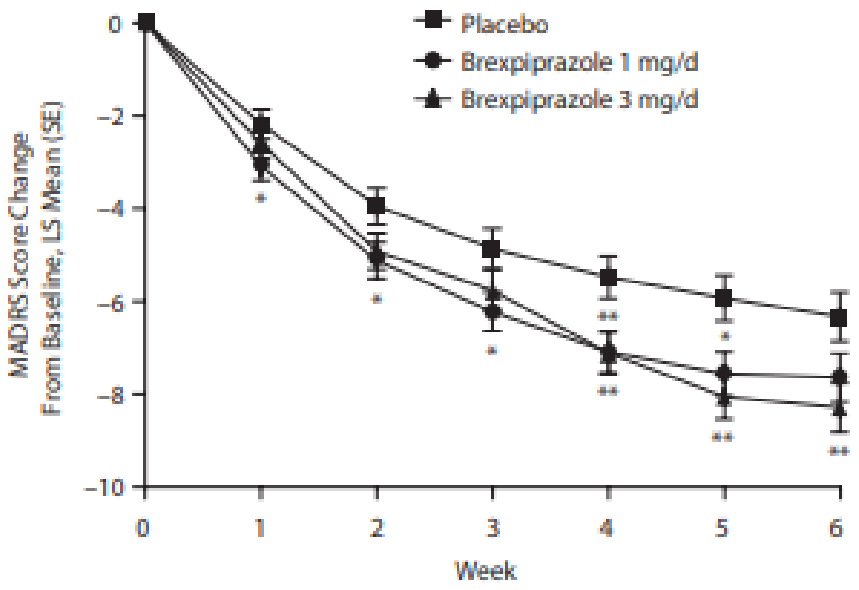


Adjunctive brexpiprazole demonstrated efficacy in patients with major depressive disorder and inadequate response to antidepressants

- **Double-blind** treatment using **adjunctive brexpiprazole 1 mg and 3 mg daily** dosing vs. adjunctive placebo
- **N=677** patients **who had an inadequate response to a 8-week single-blind placebo adjunct to** escitalopram, fluoxetine, controlled-release paroxetine, sertraline, duloxetine, or venlafaxine
- **Brexpiprazole** (n=175) **reduced mean MADRS total score versus placebo** (n = 178) **at week 6** in the efficacy population per final protocol (−8.36 vs −5.15, P = .0002). **Brexpiprazole improved SDS mean score versus placebo** (−1.35 vs −0.89, P = .0349).

Thase et al. J Clin Psychiatry. 2015a

Adjunctive brexpiprazole 1 and 3 mg for patients with mdd following inadequate response to antidepressants: a phase 3, randomized, double-blind study



- In the efficacy population per final protocol, **brexpiprazole 3 mg** (n=213) **showed a greater improvement in MADRS total score vs. placebo** (n = 203; -8.29 vs -6.33; P = .0079), **whereas brexpiprazole 1 mg did not** (n = 211; -7.64 vs -6.33; P = .0737).

- The **brexpiprazole groups showed a higher improvement in SDS** mean score versus placebo (least squares [LS] mean difference: [1 mg] -0.49, P = .0158; [3 mg] -0.48, P = .0191).

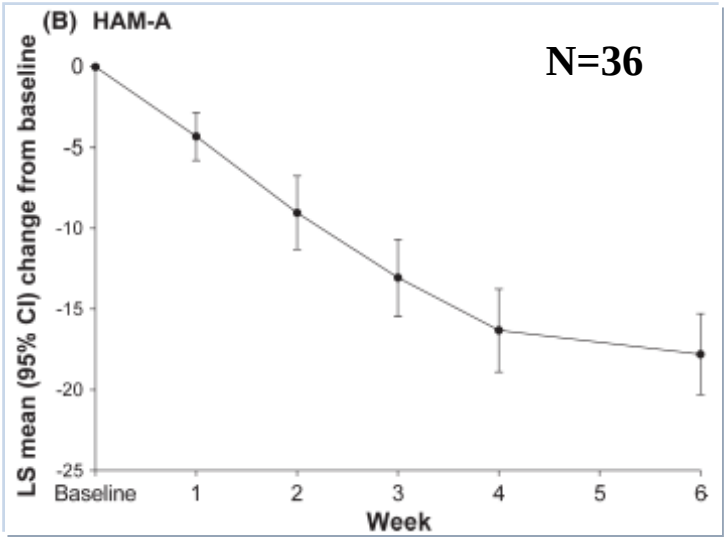
Brexpiprazole 3 mg showed efficacy *vs.* placebo in the efficacy population per final protocol. Both doses of brexpiprazole were well tolerated

Thase et al. J Clin Psychiatry. 2015b

Brexpiprazole+ADs may be an appropriate treatment option for the difficult-to-treat MDD patients with anxiety

- This is an **exploratory 6-week, open-label study** exploring the effect of brexpiprazole adjunctive medication to antidepressants

	Baseline	Change from baseline at Week 6
Scale	Mean (*SD*)	Mean (*SD*)
HAM-D-17 total score	24.50 (3.95)	−15.85 (7.37)
KSQ total score	55.9 (13.8)	−29.4 (20.9)
Symptom subscales		
Anxiety	10.6 (3.8)	−5.2 (5.1)
Depression	11.9 (3.4)	−6.6 (5.1)
Somatic symptoms	8.1 (4.9)	−4.1 (4.1)
Anger–hostility	8.6 (4.6)	−4.5 (4.5)
MGH–CPFQ total score	28.53 (4.18)	−9.85 (8.79)
BIS-11 total score	71.67 (8.99)	−7.67 (10.14)

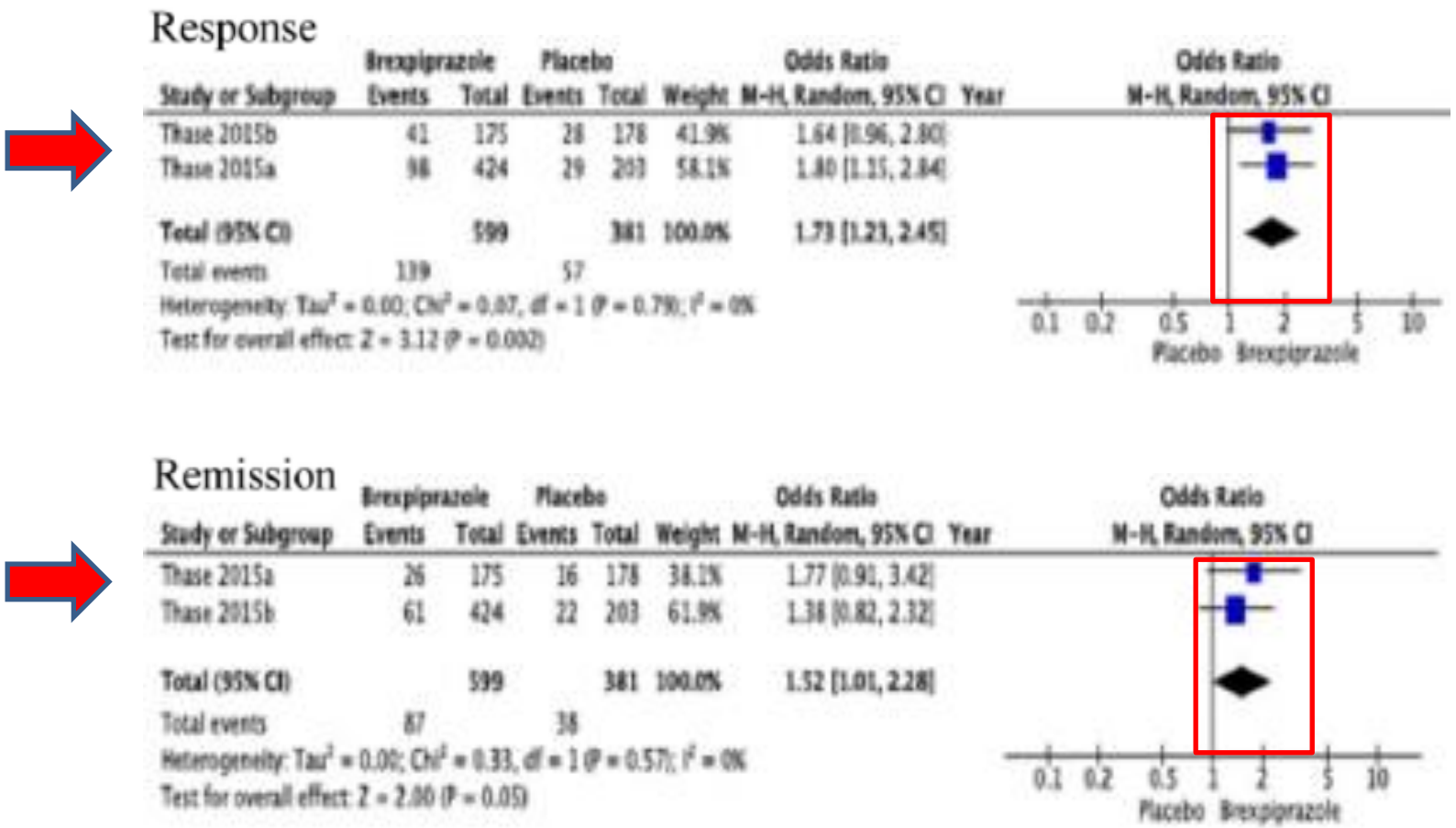


- **Improvements in depression and anxiety symptoms** were **observed <u>as early as 1 week</u> after initiation of brexpiprazole**, and followed a similar time course.

Symptoms of depression/anxiety improved in MDD with concurrent anxiety who had an inadequate response to antidepressants, following treatment with **brexpiprazole** at a **mean dose** of **2.1 mg day−1 adjunctive to ADs**

Davis et al., Brain Behav 2016;6:e00520

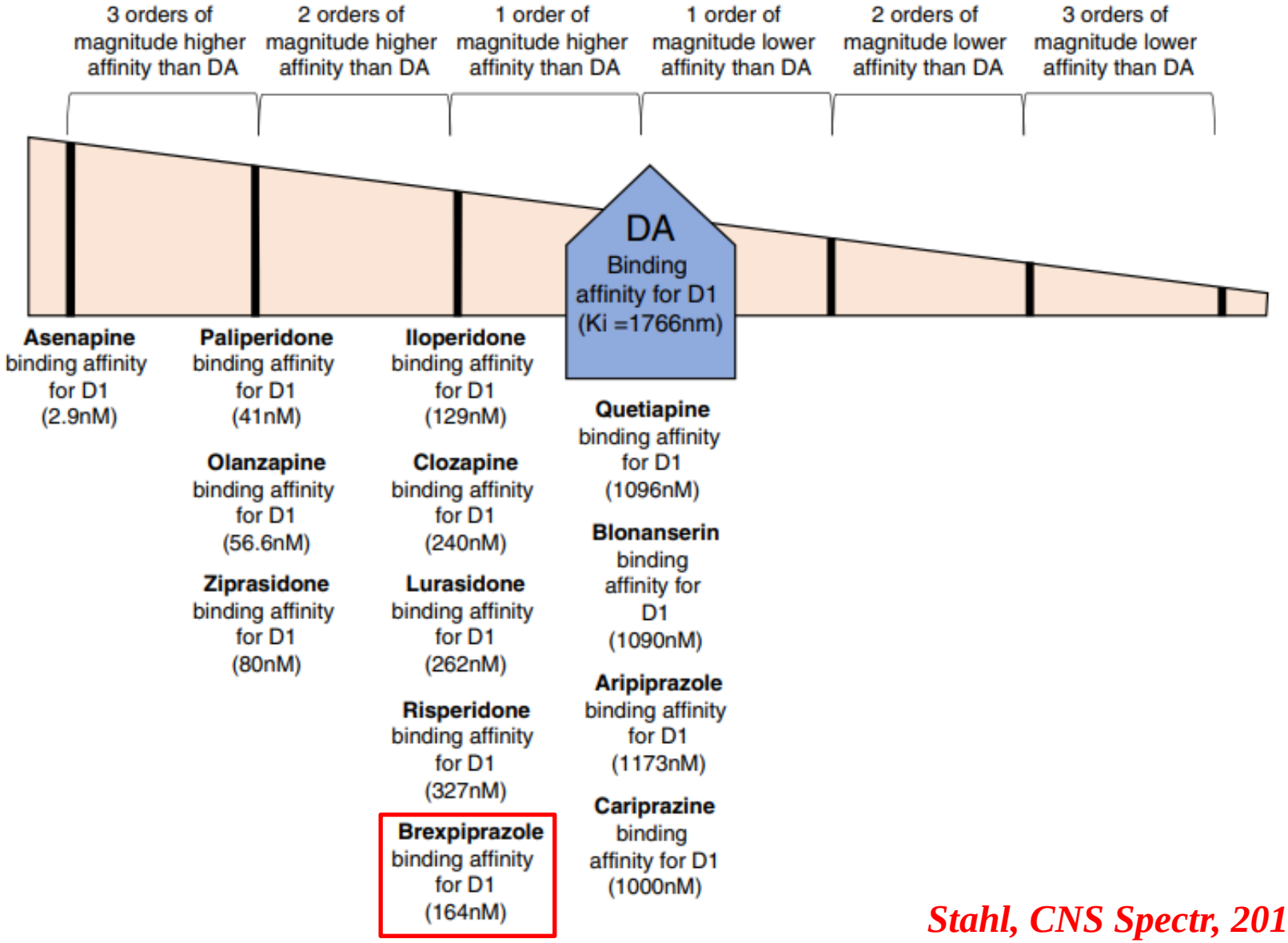
Forest plot for MDD: brexpiprazole



Improvements of response (OR: 1.73) and remission (OR: 1.52) rates were found **with brexpiprazole as an add-on to antidepressant medications**

Romeo et al., J Psychopharmacol 2018

The relative affinities of drugs for psychosis and mood for D1R compared to the affinity of dopamine itself for D1R



Stahl, CNS Spectr, 2017

Brexpiprazole may induce a rapid and potent therapeutic effect in treatment-resistant depression

- **Add-on treatment with antipsychotics to SSRIs facilitates AMPAR-mediated transmission via D1R activation**, an effect **not obtained by drugs separately**.

  (Björkholm et al., Int J Neuropsychopharmacol 2014; Eur Neuropsychopharmacol 2015)

- **Brexpiprazole** (10 nM or 3 nM) in combination **with escitalopram, potentiates EPSPs in mPFC pyramidal cells** and **forceps minor** (resembling observations with clozapine or asenapine).

  Björkholm et al., Int J Neuropsychopharmacol 2014; Chen and Yang, J Neurophysiol 2002

- Addition of **brexpiprazole to SSRIs potentiates** or **normalizes** the levels of **BDNF** and **dendritic spine density** in preclinical models

  Ma et al., Psychopharmacol.(Berl.) 2016; Hirose et al., Biol Psychiatry 2014

- **At lower doses**, **add-on** treatment with **brexpiprazole** to antidepressants **reduces depressive symptoms** and **improves social functioning in TRD**

  Thase et al., J Clin Psychiatry 2015a, b

Combination of brexpiprazole and escitalopram **facilitated AMPA-induced D1R dependent currents similarly to ketamine**

Brexpiprazole **induces** a **clozapine-like D1R dependent facilitation of mPFC NMDAR-transmission** ameliorating **cognitive deficits**

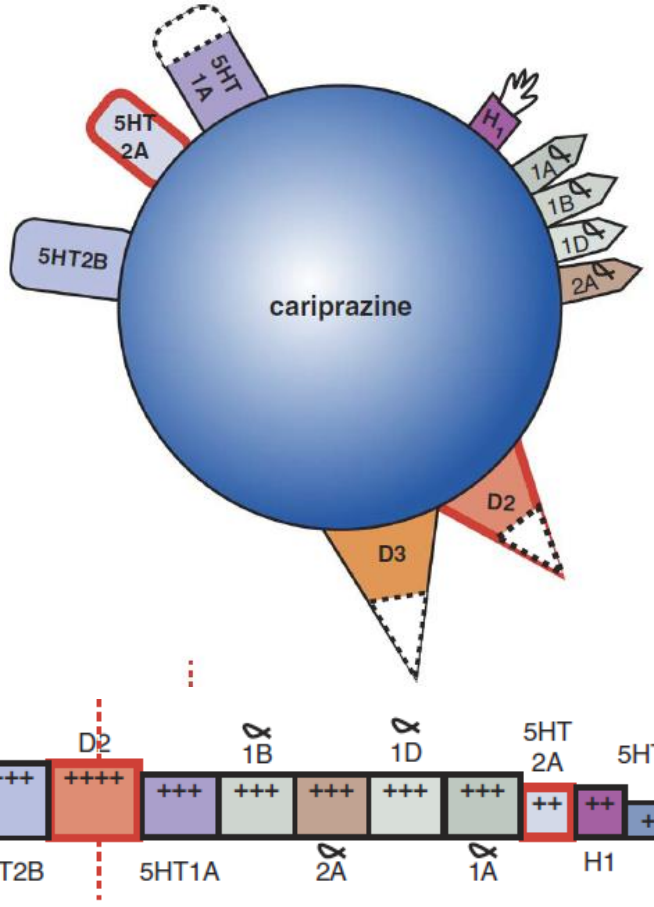
Björkholm et al., Eur Neuropsychopharmacol 2017

The third class of medications not still approved as adjunctive agents to antidepressants

Cariprazine

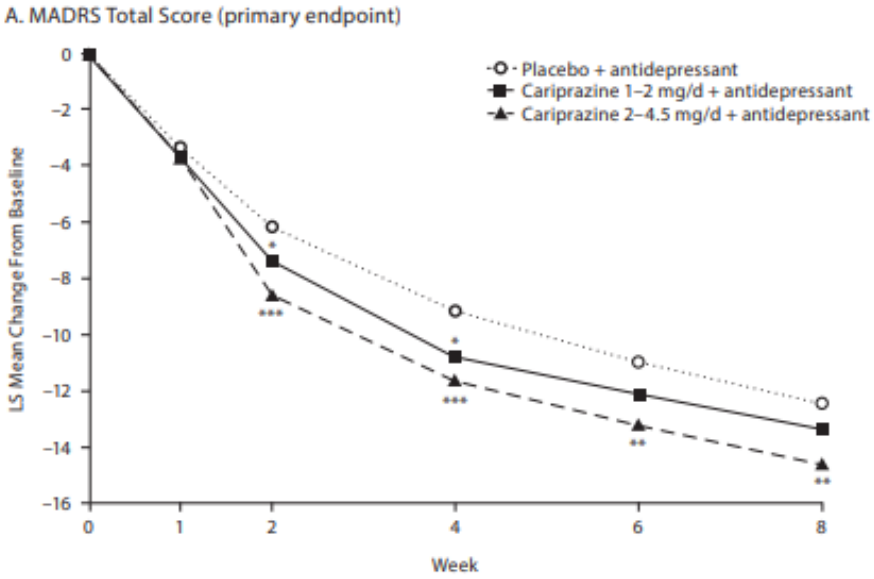
Cariprazine, a dopamine receptor–preferring **D3/D2 and serotonin 5-HT1A** receptor **partial agonist**

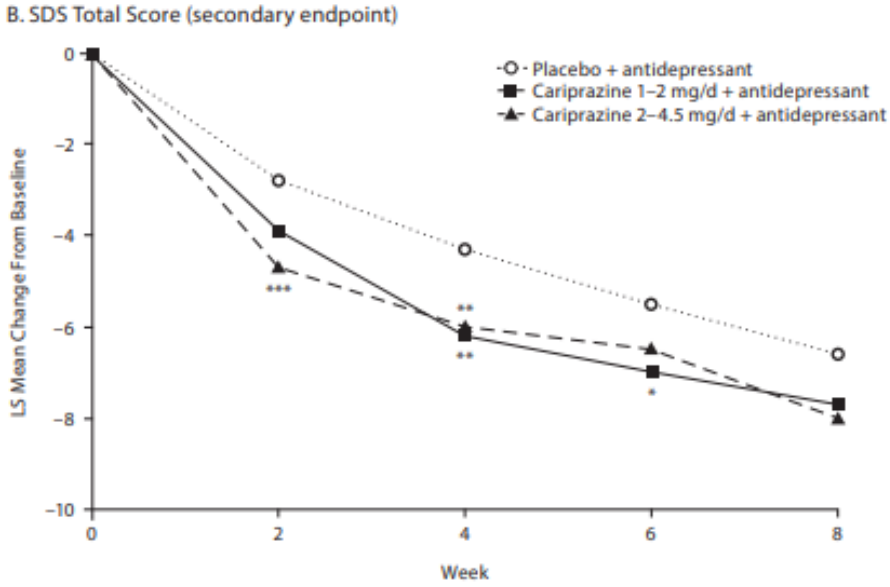
High affinity and occupancy of both D3 and D2 receptors (the highest D3 receptor binding affinity and D3 *vs.* D2 receptor selectivity (by approximately 6- to 8-fold)



Silfstein et al., Neuropsychopharmacology 2013; Kiss et al., Synapse 2011

Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: a randomized, double-blind, placebo-controlled study in MDD





2-4.5 mg/dl of cariprazine on the MADRS outcomes **at week 2** suggests a **fast onset of** treatment **effect**

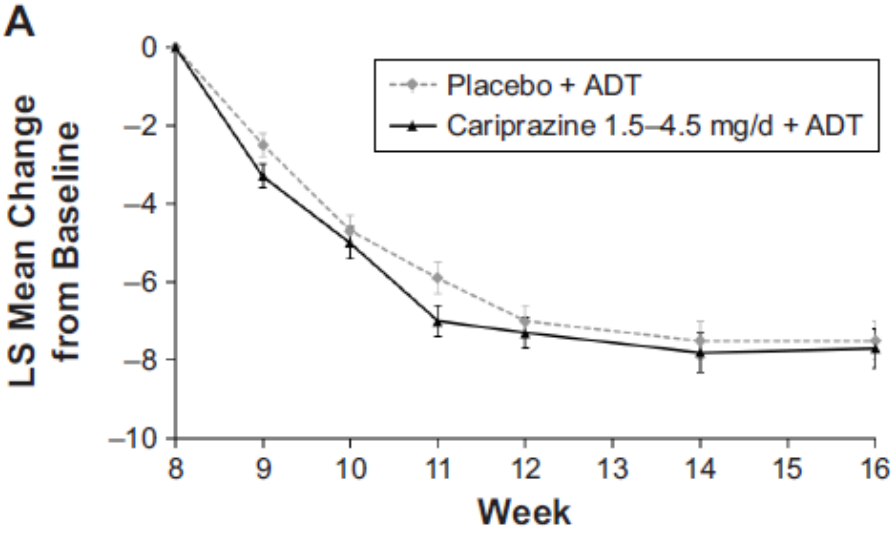
Adjunctive cariprazine 2-4.5 mg/d was **effective and well tolerated in MDD** who had **inadequate responses to** standard **antidepressants**

(Durgam et al., J Clin Psychiatry 2016)

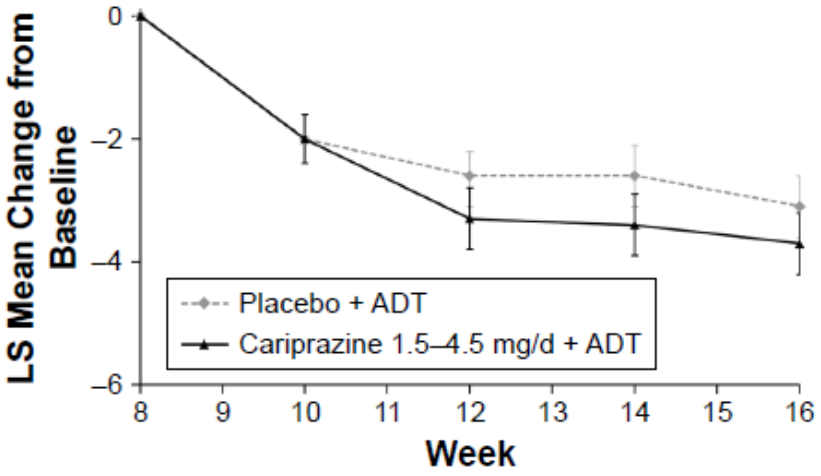
Cariprazine Augmentation to Antidepressant Therapy in Major Depressive Disorder: Results of a Randomized, Double-Blind, Placebo-Controlled Trial

By Willie R. Earley, Hua Guo, György Németh, Judit Harsányi, Michael E. Thase

Changes from Baseline by Study Visit in MADRS Total Score



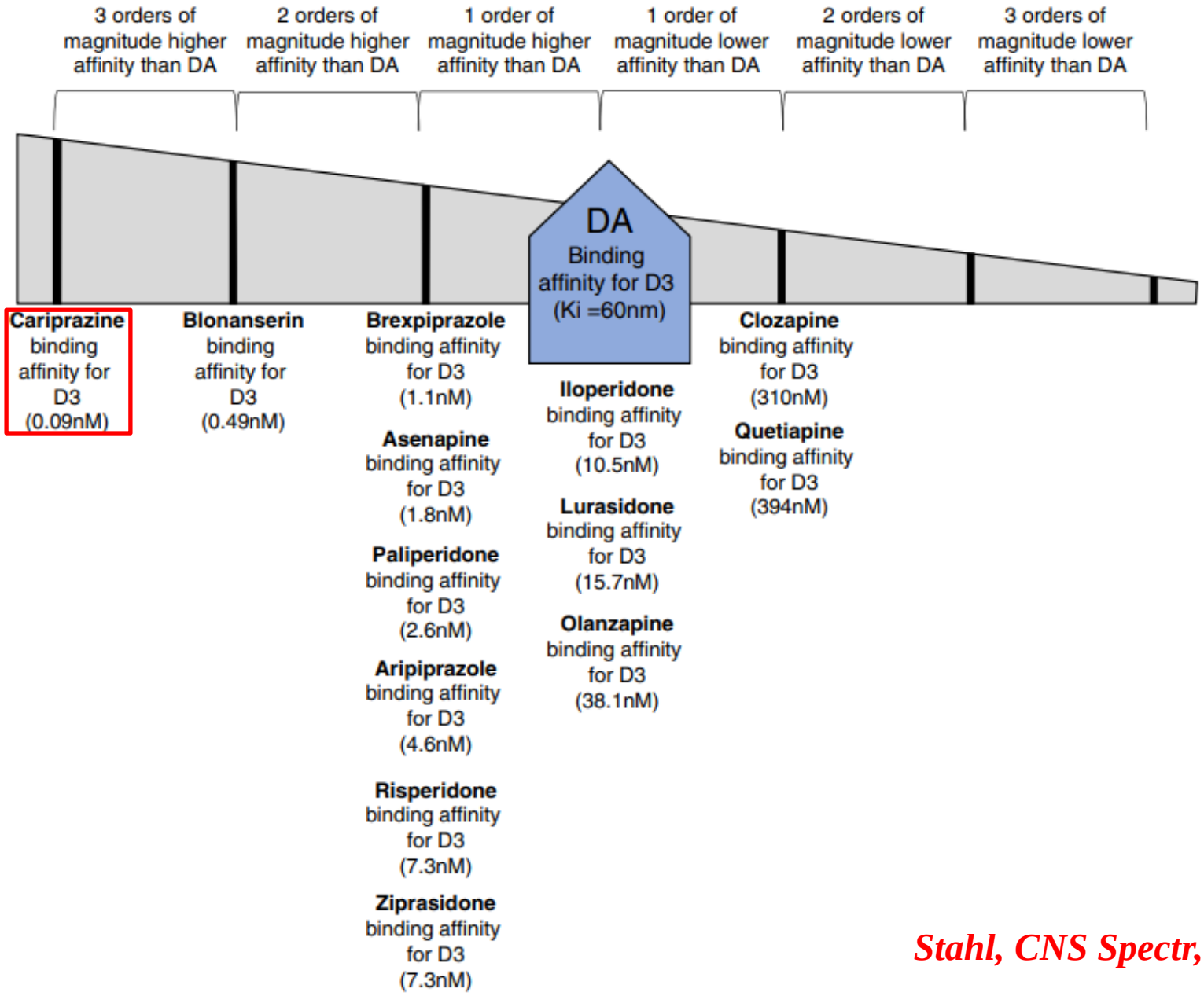
SDS Total Score Mean (Sd) Changes from Baseline by Study Visit



Adult participants with MDD and inadequate response to ADT who were **treated with adjunctive cariprazine** and ADT **did not have significant improvement in depressive symptoms** compared to placebo, but **greater reductions in symptoms** (**Sheehan Disability Scale**) compared to placebo was **observed in some efficacy measures**

(Earley et al., Psychopharmacol Bull 2018)

The relative affinities of drugs for psychosis and mood for D3R compared to the affinity of dopamine itself for D3R



Stahl, CNS Spectr, 2017

The potential involvement of dopamine D3 receptors in antidepressant-like effects occurred in specific brain regions

D3R (both post- and pre-synaptic axonal/somatodendritic autoreceptors) **was firstly discovered in** September **1990. DA binds to D3R with more than 100-fold higher affinity than D2/D1R**

(Sokoloff et al., 1990)

D3R are less sensitive to rapid phasic changes (mediating immediate salient responses) than to **slower changes (mediating the amplitude of salient responses) of** synaptic **DA levels**

(Grace, Nat Rev Neurosci 1990)

D1/D2R density is 2–3 times higher than **D3R in substantia nigra and globus pallidus (striatum). Tonic dopamine levels occupy D3R for extended periods**

(Sun et al., Plos One 2012)

D3 usually **hold back dopamine release from terminals through a negative control (directly through their autoreceptor function or indirectly through control of GABA release** which in turn **results in down-regulation of dopamine** release **in PFC and excitation of glutamate cells)**

(Carnicella et al., Transl Psychiatry 2014; Sokoloff and Le Foll, Eur J Neurosci, 2017)

The peculiar D3 location suggests interactions at glutamatergic synapses (the D3R is exacerbated when NMDAR are blocked (e.g., ketamine/phencyclidine))

(Maj et al., 1998; Lammers et al., 2000)

EJN European Journal of Neuroscience

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The dopamine D3 receptor, a quarter century later

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D3 receptors activation and antidepressant effects

1. **D3R** down-regulation or **deficiency** → **mesencephalon** → **increased incidence of depressive and cognitive symptoms of striatal functions**

(Moraga-Amaro et al., 2014; Leggio et al., Eur J Pharmacol 2013)

2. **Antidepressants** (tricyclics, SSRIs, IMAO), **ECT** → **increase the D3R expression (co-expressing D1), binding, responsiveness** → **The islands of Calleja**; **Rostral/ventromedial shell of nucleus accumbens** → **Emotional control**; **Motivation**; **Reward**

(Lammers et al., Mol Psychiatry 2000; Maj et al., Eur J Pharmacol 1998)

3. **D3R activation** → **increase neurogenesis in SVZ and striatum**

(Van Kampen and Robertson, J Neurosci 2005)

FENS Federation of European Neuroscience Societies

The novel partial dopamine D3/D2 agonist cariprazine and its pro-cognitive effects

- The **pharmacological engagement of D3** receptors **may have a positive effect on:**

1. **Cognitive performance** with D3 procognitive-like effects (through the **blockade** of **dopamine-induced inhibition** in the **hippocampus and enhancement of acetylcholine release in PFC**).

   Marder et al., Eur Neuropsychopharmacol 2016; Papp et al., Behav Pharmacol 2014; Duman et al., Am J Neuropsychopharmacol, 2012; Carnicella et al., Transl Psychiatry 2014

2. Although **other mechanisms** (e.g., **5-HT1A agonism**) **may be implicated in cariprazine's pro-cognitive effect**, the engagement of D3 receptors may provide beneficial effects in various human disorders.

   Pich and Collo, Eur Neuropsychopharmacol 2015; Rogoz et al., Pol J Pharmacol 2004

Targeting D3 receptors **may improve** negative/depressive cognitive-related symptoms (e.g., **motivation**, **anhedonia) and social behaviors**

Gross and Drescher, Handb Exp Pharmacol 2012; Nakajima et al., Eur Neuropsychopharmacol 2013; Papp et al., Behav Pharmacol 2014

The anxiolytic and antidepressant-like effects of the novel D3/D2 agonist cariprazine

The **antianhedonic-like actions** of cariprazine were **not observed in D3-KO mice**

Duric et al., Int J Neuropsychopharmacol, 2017

This indicates that…

dopamine **D3 receptors are required to mediate the antidepressant-like effects** of cariprazine

The **anxiolytic actions** of cariprazine were **not observed** in **D3-KO mice**

Steiner et al., Physiol Behav 1997

This suggests that…

blockade of **D3** receptors in the brain **may produce anxiolytic effects**

7-OH-DPAT and cariprazine (are both preferential D3R agonists) were **found to exert anxiolytic- and antidepressant-like effect** in both rats/mice models and clinical application

(Marder et al., Eur Neuropsychopharmacol 2019; Duric et al., Int J Neuropsychopharmacol 2017; Rogoz et al., Pol J Pharmacol 2004)

D1/D3R polypharmacology as a potential treatment for substance abuse: the crucial role of D3 in the control of reactivity to drug-linked cues (drug-seeking behaviors)

The D3 receptor partial agonists

may attenuate the effects of:

cocaine (Duarte et al., Neuropsychopharmacology 2003; Cervo et al., Pharmacol. Biochem. Behav. 2005)

morphine (Frances et al., Neuroreport 2004; Duarte et al., Neuropsycho-pharmacology2003)

amphetamine (Aujla and Beninger, Behav Pharmacol 2005)

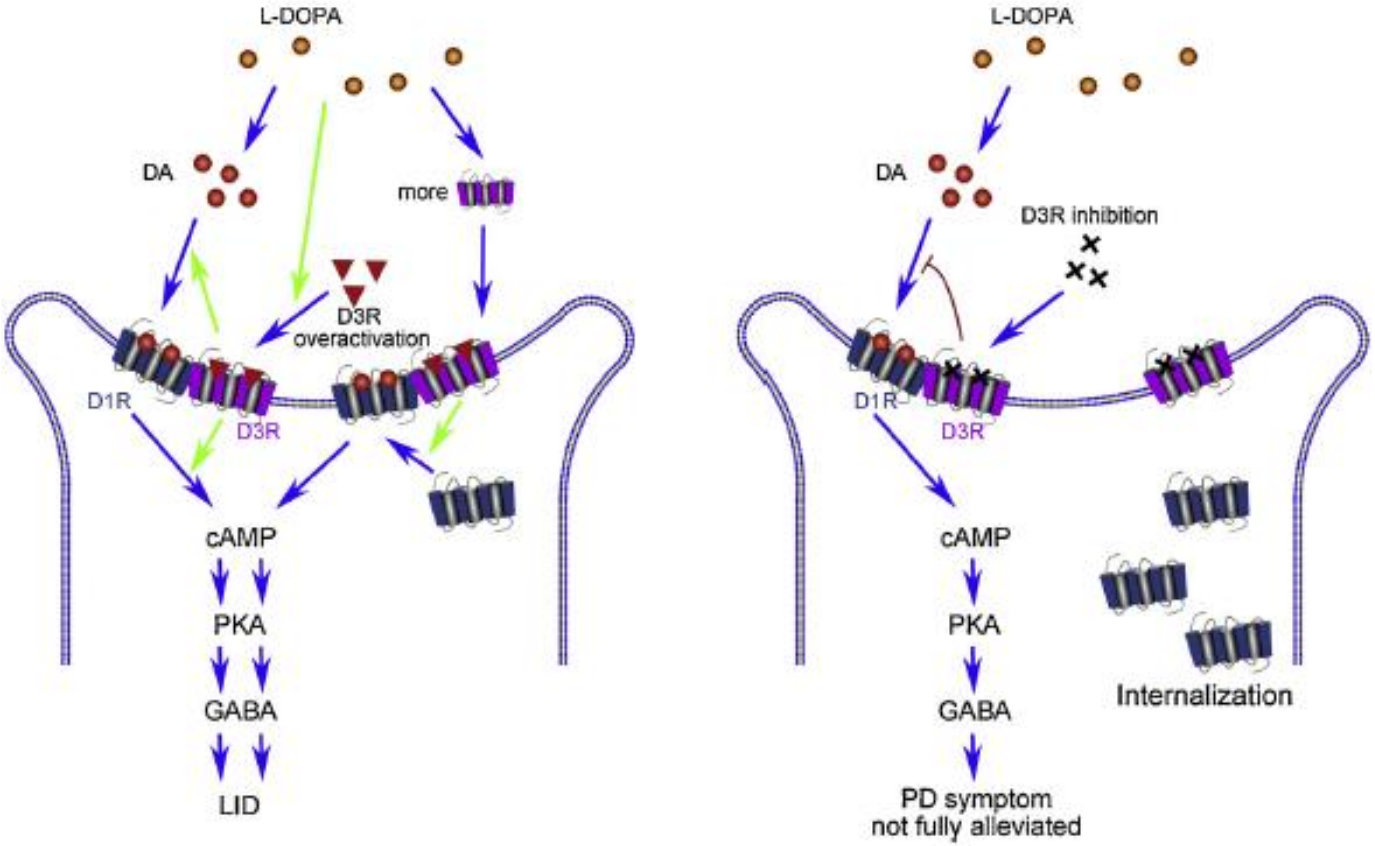
nicotine (Le Foll et al., Mol. Psychiatry 2005)

..as the potencies of partial agonists were **found to correlate with D3 but not D2..**

..D3 (through **a tonic inhibition on the ventral tegmental area) potentiates D1-induced** stimulation of **GABA release..**

Galay et al., Neurosci Biobehav Rev 2018; Sokoloff and Le Foll, 2017

The cross-talk between D3R and D1R



1. **D3R enhances D1R expression**, **increases the affinity of DA to D1R**, and activates the D1R signal pathway, **inducing D1R oversensitivity leading to dyskinesia**

2. **L-dopa induces D1-BDNF mediated D3 expression (upregulation), and** drug-induced **dyskinesia.**

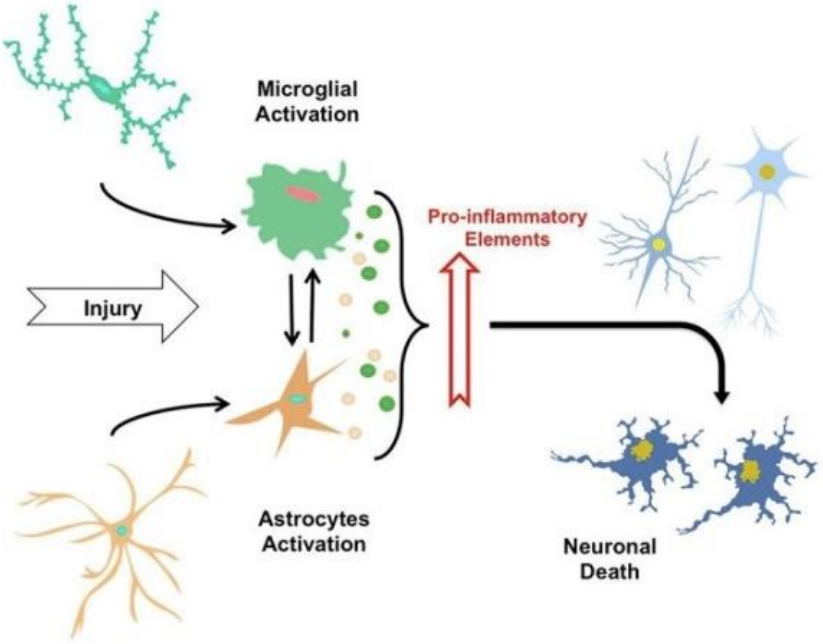
3. **D3R inhibition relieves dyskinesia,** and **leads to decreased affinity of DA on D1R**

Yang et al., Ageing Research Reviews 2020; Sokoloff and Le Foll, Eur J Neurosci, 2017

The modulatory role of dopamine receptors in brain neuroinflammation

The **differential activation of DAR is able to control tissue inflammation and injury**

The anti-inflammatory effect of DAR is closely **related to the inhibition of NF-κB activation through** protein **phosphatase 2A (PP2A)-dependent Akt pathway**



Recently, the role of DAR in neuro-inflammation has been investigated widely

Ponomarev et al., Front. Immunol 2018; Han et al., Br. J. Pharmacol. 2017; Zhang et al., 2016

At the beginning of a fashinating journey…

Only further experience with partial agonists in practice **will answer the question of what are the clinical correlates of preferentially binding D1, D2, D3 receptors …….**

Stephen Stahl

Sthal, CNS Spectrums (2016), 21, 123–127