5-HT2A agonist drugs as new treatments in psychiatry

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Importance of serotonin 2A receptor

**Majority of research on tryptamine psychedelics**

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<th>DMT</th>
<th>Psilocin</th>
<th>LSD</th>
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**[¹⁸F]Altanserin**

**Hot colours** = expression of serotonin receptor (PET imaging, Erritzoe et al.)

Correlation between 2A affinity & potency (Glennon et al. 84)

2A antagonism attenuates key psychological effects (Vollenweider et al.; Preller et al. 16; Riba et al.)
Word on the street?

Therapeutic promise

• Obsessive compulsive disorder  (Moreno et al. 06)
• Depression  (Carhart-Harris et al. 16; Osorio et al. 15)
• End of life anxiety  (Grob et al. 12; Gasser et al. 14... Ross et al.; Griffiths et al.)
• Alcohol dependence  (Bogenschutz et al. 15)
• Tobacco addiction  (Johnson et al. 14)
• Wellbeing ↑ Optimism ↑  (Griffiths et al.; Carhart-Harris et al.)

Limitations?

• Psychological distress and suicidality ↓  (Hendricks et al. 15)
• ‘Flashbacks’ very rare  (Halpern & Pope, 2003; Carhart-Harris & Nutt, 10)
• Prolonged neg psych reactions v rare  (Cohen & Ditman, 1962; Studerus et al.)
• Anxiety/dysphoria in acute state is dose-dep’  (Griffiths et al. 06, 11)
• Transient headaches common  (Johnson et al. 14; Carhart-Harris et al. 16)
Preclinical work:
5-HT2AR agonism, cognition & learning

5-HT2AR agonism $\uparrow$ cognitive flexibility & learning $\uparrow$
(King et al. 1974; Harvey et al. 03; Romano et al. 10; Zhang & Stackman, 15)

Normal BDNF (vehicle)  
2A agonism $\rightarrow$ BDNF $\uparrow$

Vaidya et al. 97

5-HT2AR agonism $\uparrow$ cortical plasticity $\uparrow$
(Vaidya et al. 97; Gerwitz et al. 02; Fankel et al. 02)
Psychodelics & cognition in humans?

Ayahuasca → Creative/divergent thinking ↑
(Kuypers et al. 16; Frecska et al. 12;)

LSD → imaginative suggestibility ↑
(Carhart-Harris et al. 15)

DA & 5-HT
What do these neuromodulators modulate?

Focus
DA
Stimulants
e.g. modafinil

Flexibility
5-HT
Psychodelics
e.g. LSD

Inverse ‘U’ for both systems:
Excess confidence (DA) or flexibility (5-HT) → mania/psychosis?
Psychedelics & mood

MDMA, psilocybin & LSD → positive mood [state] ↑
(Carhart-Harris et al. 14, 16, Schmid et al. 15)

Psilocybin & LSD → optimism [trait] ↑
(Carhart-Harris et al. 15 & 16)

5-HT2AR antagonism attenuates positive mood effects of MDMA & psilocybin
(Van Wel et al. 12; Kometer et al. 12)

5-HT & mood

Post-syn’ 5-HT1AR agonism → impulsivity & stress ↓

Cortical 5-HT2AR agonism → cog flexibility ↑ emo’ lability ↑

“We feel good when we ‘go with the flow’”  
(Adrian Bejan)

[2A mediated?]
Psilocybin for depression

- Open label feasibility study (n = 20)
- Treatment resistant major depression
- Two doses of psilocybin (10mg + 25mg) separated by 1 week
- Pre & post fMRI
Rapid & long-term decreases in depressive symptoms

**Well tolerated. All showed reductions 1w post. 9/19 in remission at 3w.**

\( p < 0.001 \) BL v all time-points.

Carhart-Harris et al. 2016. Lancet Psychiatry
Anxiety, anhedonia, dysfunctional attitudes, rumination ↓

“I felt a greater sense of calm.”

“I’ve seen a much clearer picture.”

“After my experience, it felt as world became more bright and colourful and I could enjoy every little thing.”
Subjective optimism

1) In uncertain times, I usually expect the best, 2) If something can go wrong for me, it will, 3) I’m always optimistic about my future, 4) I hardly ever expect things to go my way

“My outlook has changed significantly. I'm more aware now that it's pointless to get wrapped up in endless negativity. I feel as if I've seen a much clearer picture.”

[Patient from depression trial, male, aged 52, >20yrs depression]
Decreased CBF one-day post 25mg AMG CBF ↓ correlated with QIDS ↓ baseline v post-treatment

AMG CBF in MDD, e.g. Drevets et al. 92

$Z = 2.3, p < 0.05$

$R = 0.59$

$P = 0.02$
Neural correlates of psilocybin ‘after glow’: vmPFC RSFC

Increased vmPFC RSFC predicts response at 5 weeks (QIDS)

Consistent with ECT, e.g. Mulders et al. 16
Increased AMG BOLD response to fear faces one-day post treatment

Increased AMG BOLD response to happy faces too

AMG BOLD response to F v N
Remitters (F v N) > non-remitters (F v N)

Opposite to SSRIs, e.g. Ma et al. 15

Greater amygdala responsiveness
Acute brain effects of psychedelics: Increased global functional connectivity

Petri et al. 15 (psilocybin); Tagliazucchi et al. 16 (LSD)

“The feeling of no boundaries. Somehow I was able to comprehend what oneness is.”

Stace (1975); Griffiths et al. (2006, 08, 11)
How do 5-HT2AR agonists work in depression?

- Cognitive flexibility ↑ Wellbeing & optimism ↑?
- Mystical experience ↑ psychological wellbeing ↑ (Griffiths et al.; Bogenschutz et al.)
- Mystical experience ↑ depressive symptoms ↓ (Carhart-Harris et al.)

Useful analogies?

Calm after storm

A broader perspective

A reset
What is the 5-HT2AR for?

Change!
“Those who cannot change their minds, cannot change anything.”

George Bernard Shaw, Irish playwright (1856-1950)
Change is never painful, only the resistance to change is painful

— Gautama Buddha —
“Your assumptions are your windows on the world. Scrub them off every once in a while, or the light won't come in.”

Isaac Asimov, writer & biochemist (1919-1992)
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