# An exploration of the antidepressant potential of the 5-HT$_4$ agonist, prucalopride, in the healthy human brain

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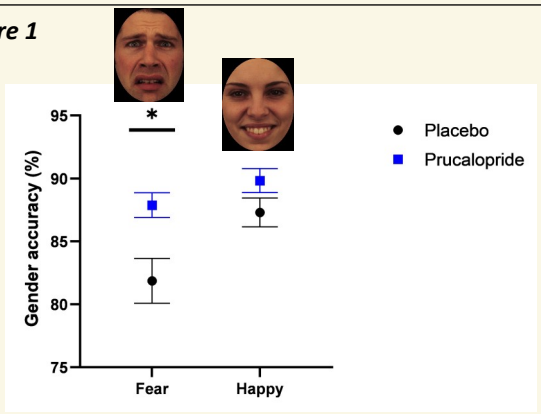
## Introduction:

Most patients starting antidepressants experience a therapeutic delay[1]. Animal studies suggest selective 5-HT$_4$ (fourth serotonin) receptor stimulation leads to rapid serotonin release and production of neurotrophic factors. Therefore, 5-HT$_4$ receptor agonism may be a target for rapidly-acting antidepressant treatment[2] as well as improving cognition[3].

We examined whether 6 days of the licensed 5-HT$_4$ partial agonist, prucalopride, affected behavioural and neural emotional processing in healthy humans, using an experimental medicine model shown to predict antidepressant activity after a few doses.

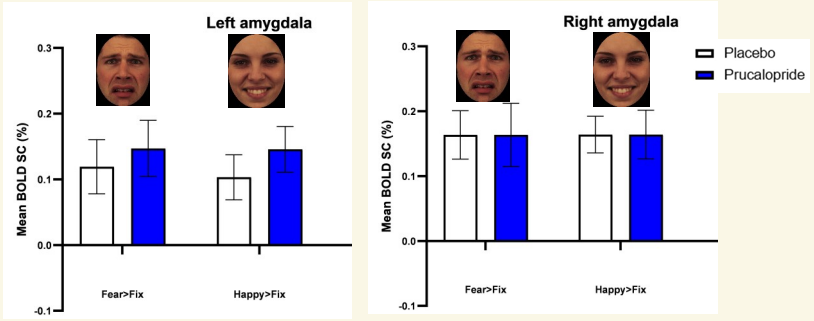
**Hypothesis: Prucalopride would show, similar to other serotonergic antidepressants, decreased response to negative vs. positive emotional stimuli (i.e. prucalopride reducing activation in the amygdala for fearful faces)**

***Figure 1***




*Accuracy (T-test) to gender discrimination task as part of fMRI faces paradigm. Error bars show standard error of the mean. *=p<0.05*

***Figure 2***




*Group mean of BOLD percentage signal change extracted from L & R amygdala (Harvard-Oxford atlas 90% threshold) to fearful & happy images. Error bars show standard error of the mean.*

## Methods:

Right-handed healthy participants were randomised to either prucalopride (6 days x 1mg) or placebo, in a double-blind design. Drug allocation was stratified for gender. The study had ethical approval (MSD-IDREC R57219/RE001) and clinicaltrials.gov preregistration (NCT03572790).

On day 6, participants underwent a 3T scan including an fMRI emotional processing task. Imaging data were analysed with FSL, and were corrected for multiple comparisons. Brain activations showing significant group differences were identified using cluster-based thresholding (Z>3.1, p<0.05 corrected). Regions of interest analyses were pre-specified.

## Results: 5-HT$_4$ agonism versus placebo (N=43, 18-40y)

⇒ Participants receiving prucalopride were more accurate at identifying the gender of faces overall [F(1,41) =7.47, p=0.009, np$^2$=0.15], driven predominately by response to fearful faces (Figure 1).

⇒ Whole brain analyses: prucalopride reduced activation in 6 regions corresponding to the default mode network (DMN) (Figure 3A).

⇒ Region of interest analyses: prucalopride reduced activation in the anterior cingulate cortex (hub of the DMN) (Figure 3B).

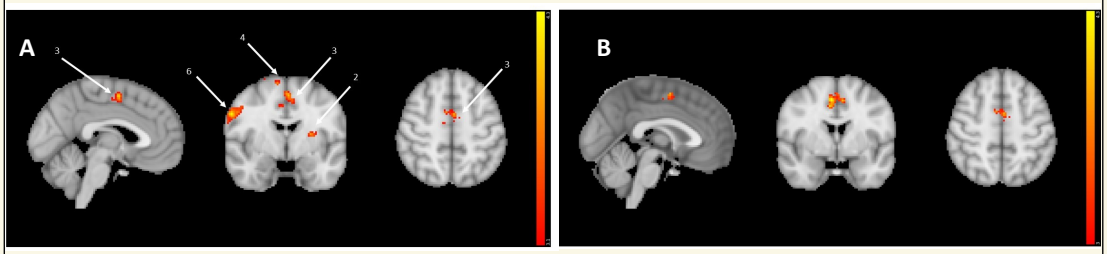
⇒ Prucalopride was <u>not</u> associated with a difference in amygdala activation for fearful versus happy faces (Figure 2).

Results were unaffected by gender / grey matter / perfusion.

## Conclusions:

**Our investigations do <u>not</u> suggest an antidepressant-like profile for prucalopride in humans,** but further studies should consider a wider dose range. **However, our study provides support for a pro-cognitive effect** of 5-HT$_4$ receptor agonism in humans, with further evidence of behavioural and neural mechanisms.

***Figure 3***




***<u>A</u> Whole-brain activation for 6 regions to mean effect of task in placebo vs. prucalopride group depicting significantly increased activation in placebo group. <u>B</u> Region of interest activation for anterior cingulate cortex to mean effect of task in placebo vs. prucalopride group depicting significantly increased activation in placebo group. All sagittal, coronal and axial images shown at MNI location 45,61,62. Images thresholded at z> 3.1 p<0.05 corrected. Scale Z=3.1 to 4.3.***

## References:

[1] Duman 2007, Neuron, 55 (5) 679-681
[2] Lucas et al 2007, Neuron 55(5):712-725
[3] de Cates et al 2021, Transl Psychiatry 11, 497