Drugs for schizophrenia – the story beyond dopamine

Paul Morrison
Institute of Psychiatry
“Only a fool would imagine it was possible to ride from Bordeaux to Paris on just water…”

Leave me in peace, we all take dope”.

“It was obvious for me that finding a treatment for amphetamine intoxication would provide a cure for paranoid schizophrenia…”

“Quicker than expected the compound haloperidol did the trick. The next step was to test the effect on a human being…”

“Dr Bobon in Liège introduced me to a 16 year old boy, showing all the symptoms of paranoid schizophrenia. Dr Bobon agreed to give him haloperidol and he calmed down; the effect was amazing…”
Glutamate Therapeutics

- Based on the psychotomimetic effects of ketamine

Positive & **negative** symptoms (?)

- Two candidate therapeutic mechanisms

  1. Boost glycine
  2. Inhibit glutamate release

Direct agonists: *e.g.* glycine, *D*-cycloserine

Glycine re-uptake inhibitors: *e.g.* sarcosine, **Bitopertin**

Metabotropic glutamate receptor group II agonists: *e.g.* **LY-2140023**
1. Boosting the glycine site of the NMDA channel

Glycine, serine, D-cycloserine or sarcosine

Efficacy?

1. Small proof of concept trials (n=10-60)  YES

2. Larger RCT's (n=157, 190) 16 weeks  FAIL x 2

3. Meta-analyses  YES

CLASS: Glycine re-uptake inhibitor

**Bitopertin**

<table>
<thead>
<tr>
<th>Preclinical Tests</th>
<th>Anti-psychotic signature</th>
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<td>PCP induced hyperlocomotion</td>
<td>YES</td>
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<td>Amphetamine induced hyperlocomotion</td>
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CLASS: Glycine re-uptake inhibitor

Bitopertin

Clinical Trial

2010 RCT (Adjuvant BITOPERTIN v PLC) for negative symptoms n=323, 8 weeks

Efficacy?

YES

6 large RCT's (n =3600)
- 3 on negative symptoms
  FAIL x 3
- 3 on sub-optimally treated positive symptoms
  FAIL x 2
2. Inhibiting glutamate release

CLASS: Metabotropic glutamate receptor group II agonists

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<td>Conditioned Avoidance</td>
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Increases dopamine release in the frontal cortex: BONUS (?)
2. Inhibiting glutamate release

CLASS: Metabotropic glutamate receptor group II agonists

LY-2140023

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<tr>
<td><strong>2007</strong> RCT (LY v OLANZ v PLC) n=196, 4 weeks</td>
<td>YES</td>
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<td><strong>2011</strong> RCT (LY v OLANZ v PLC) n=853, 4 weeks</td>
<td>Inconclusive</td>
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<td><strong>2013</strong> Randomised open label (LY v atypical D2) n=261, 24 weeks</td>
<td>FAIL</td>
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<td><strong>2013</strong> RCT (Adjuvant LY v placebo) for negative symptoms n=167, 16 weeks</td>
<td>FAIL</td>
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<td><strong>2014</strong> RCT (LY v aripiprazole) n=678, 24 weeks</td>
<td>FAIL</td>
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Where now for glutamate drugs in schizophrenia?
Other Candidates

CLASS: Phosphodiesterase inhibitors (PDE10A)

MP10, PF-2545920

- Animal studies predict antipsychotic effects.

- But first RCT: RISP v PF
  (n>200; 4 weeks) FAIL
### Other Candidates

**Alpha7 nicotinic receptor agonists**

- Association between P50 deficit and alpha7 nicotinic gene
- Alpha7 stimulation → Increased prefrontal Dopamine release

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**TC-5619**

| 2013 RCT (TC vPLC) add-on to D2 drug. | Improved cognition |
| N=185, 12 weeks | Improved negative symptoms |

**Targacept, Inc.**

| 2013 RCT (TC vPLC) add-on to D2 drug. | Cognition: **FAIL** |
| N=477, 24 weeks | Negative symptoms: **FAIL** |
|  | **Programme dropped.** |

**EVP-6124**

**EnVivo Pharm.**

| 2011 RCT (EVP vPLC) add-on to D2 drug. | Improved cognition |
| N=319, 12 weeks | Improved negative symptoms |

**Phase III trials ongoing**

**RG3487**

**Memory Pharm.Roche**

| 2014 RCT (RG vPLC) add-on to D2 drug. | Cognition: **FAIL** |
| N=215, 8 weeks | Improved negative symptoms |
Other Candidates

CLASS: Nitric Oxide Donors

Sodium nitroprusside (SNP)

- **SNP** inhibits PCP effects in animals.

- First RCT: (IV **SNP** v PLC) 1 injection
  n=20, follow-up over 4/52

Rapid and sustained improvement.
Other Candidates

CLASS: Nitric Oxide Donors

Sodium nitroprusside (SNP)

- SNP inhibits PCP effects in animals.
Other Candidates

CLASS: Cannabinoid

Cannabidiol (CBD)

- **CBD** inhibits THC psychosis in humans.

- First RCT: (**CBD** v Amisulpride)
  n=42, 4 weeks

CBD = Amisulpride
Other Candidates

CLASS: Cannabinoid

Cannabidiol (CBD)

- CBD inhibits THC psychosis in humans.
The BRC are currently recruiting for a range of trials. The team provides more details on a range of pharmaceutical and psychosocial interventions. If you would like to refer your patient for a study, or hear more about the BRC, please get in touch:

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biomedical-research-centre

ONGOING:

- SNP
- CBD
- Alpha7 nicotinic agonists
- Minocycline