**Table 15: Summary table**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **Pharmacology** | **Type of evidence** | **Efficacy findings** | **Side-effect profile** | **Evaluation of evidence according to GRADE framework** (Siemieniuk, Guyatt 2019) | **Overall quality of evidence**  |
| **Cariprazine**  | Partial dopamine D2/3 receptor agonist with very high D3 affinity | 5 Short-term RCTs1 Meta-analysis2 Maintenance studies | * Meta-analyses estimate mean difference in PANSS is between -6.23 and -9.71 over 6 weeks, similar to existing antipsychotics
* Potential benefit for negative symptoms in patients with persistent negative symptoms
 | * Generally favourable side-effect profile with low risk of metabolic side effects
* 10% incidence of EPSEs
 | * Inconsistency- NCT00404573 did not find significant difference between comparator groups
 | Moderate |
| **Brexpiprazole** | Partial dopamine agonist | 5 Short-term RCTs1 Maintenance study  | * Inconsistent results: 3 RCTs had positive findings, in 2 RCTs brexpiprazole failed to separate from placebo
* May improve social functioning
 | * Lower incidence of akathisia than aripiprazole and cariprazine
* Minimal metabolic side effects
 | * Inconsistency- 3 RCTs had positive results at specific brexpiprazole doses
 | Moderate |
| **Brilaroxazine****(RP5063)** | High-affinity D2, D3 and D4 receptorpartial agonist  | 1 RCT | * Brilaroxazine 15mg and 30mg groups had statistically significant reductions in PANSS compared to placebo in 1 RCT
 | * EPSEs
* Akathisia
* Elevated liver enzymes
* No metabolic changes
 | * Risk of bias- higher drop out rate in brilaroxazine 30mg group
* Imprecision- only 1 published RCT so far
 | Very low |
| **Lumateperone (ITI-007)**  | High affinity 5HT2A and low-moderate D2 antagonist plus serotonin transporter inhibition | 3 RCTs1 Maintenance study | * Inconsistent results: 2 RCTs had positive findings, 1 negative RCT
* Some results suggest improvement of social functioning and depressive symptoms
 | * 24% incidence of sedation
* 6.7% incidence of EPSEs
* No metabolic changes
 | * Inconsistency- 2 of 3 RCTs had positive findings but only at specific lumateperone doses
 | Low |
| **F17464** | Very high-affinity D3 antagonist and 5-HT1A partial agonist | 1 RCT | * Efficacy of F17464 on overall and positive symptoms in 1 RCT, with some indication of benefit on cognitive symptoms
 | * Insomnia (10.4%)
* Agitation (7.5%)
* Hyperlipidaemia (7.5%)
* Akathisia (4.5%)
 | * Risk of bias- 19 subjects with protocol deviations
* Imprecision- only 1 published RCT so far
 | Very low |
| **Lu AF35700** | Dopamine D1, 5HT2A and 5-HT6 receptor antagonist | 2 RCTs | * No statistically significant difference between treatment and olanzapine/risperidone groups in 2 RCTs in patients with treatment resistant schizophrenia
 | * Headache (8.2% in long term study)
* More data needed regarding cardiometabolic effects
 | * Indirectness- no placebo-controlled studies to date, only tested in treatment resistance
* Imprecision- only 2 published RCTs so far
 | Low  |
| **Pimavanserin (ACP-103)** | Inverse agonist on 5HT2A receptor, negligible action on D2  | 2 RCTs | * No published data, a press release indicates improvement in negative symptom scores
 | * No increased rates of EPSEs over placebo
* Potential to prolong QTc
 | * Inconsistency- only 1 RCT with positive findings
* Imprecision- only 2 RCTs
* Risk of bias- results not formally published in peer published journal, only as press release on drug company website
 | Very low |
| **Roluperidone****(MIN-101)** | 5HT2A antagonist, no data indicating action on D2 | 3 RCTs | * One RCT has shown a statistically significant improvement in negative symptoms, while two RCTs showed no significant difference in total symptoms between roluperidone and placebo groups
 | * No increased rates of EPSEs over placebo
 | * Inconsistency- only 1 RCT with positive findings
 | Low |
| **Ulotaront (SEP-363856)** | TAAR1 agonist with some affinity for 5HT1A receptors | 1 RCT1 Maintenance study | * One RCT and one maintenance study so far have indicated its efficacy for total symptoms and positive and negative sub-scales
 | * No increased rates of EPSEs
* No metabolic changes
 | * Risk of bias- low placebo response in RCT
* Imprecision- only 1 published RCT so far
 | Very low |
| **Xanomeline****(+ trospium)** | Muscarinic M1 and M4 agonist with no D2 affinity but functional dopamine antagonism | 1 RCT1 Pilot study  | * One phase 2 RCT indicates its efficacy on positive and negative symptoms
* Participants in the treatment arm of the pilot study showed improved positive, negative and cognitive symptoms
 | * Gastrointestinal side effects
* No increased rates of EPSEs
* No metabolic effects
 | * Risk of bias- cognitive outcomes not adjusted for multiplicity testing
* Imprecision- only 1 published RCT so far
 | Low |
| **BI 409306**  | Phosphodiesterase 9A inhibitor  | 1 RCT | * No statistically significant difference in cognition in treatment and placebo arms of 1 RCT
 | * Visual symptoms (11.1%)
* Nasopharyngitis (3.2%)
* Nausea (2.6%)
* Dizziness (2.6%)
 | * Imprecision- only 1 published RCT so far
 | Very low |
| **BI 425809** | Glycine transporter 1 inhibitor | 1 RCT | * Small statistically significant improvement in cognition in treatment arm of 1 RCT, though no improvement in functional outcomes
 | * Headache (8-12%)
* Somnolence (2-6%)
* Gastrointestinal symptoms (2-11%)
* Anaemia (1-5%)
 | * Imprecision- only 1 published RCT so far
 | Very low |
| **MK-8189** | Phosphodiesterase 10A inhibitor | 1 RCT | * No statistically significant difference between MK-8189 and placebo groups in 1 RCT
 | * Tolerability results not yet published
 | * Imprecision- only 1 published RCT so far
* Risk of bias- results not formally published in peer published journal, only on clinicaltrials.gov
 | Very low |