**Table 15: Summary table**

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| **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 RCTs  1 Meta-analysis  2 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 RCTs  1 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 receptor  partial 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 RCTs  1 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 RCT  1 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 RCT  1 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 |