Novel and emerging treatments for schizophrenia: Beyond postsynaptic dopamine receptor blockade

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Despite the discovery of chlorpromazine as the first effective antipsychotic 68 years ago and substantial pharmacologic advances, to date, postsynaptic dopamine blockade remains the sole mechanism of action of approved drugs for schizophrenia. Current dopamine modulating first-generation and second-generation antipsychotics target mainly positive symptoms, but not/inadequately negative and cognitive symptoms. Additional challenges include non-adherence and adverse effects, especially cardiometabolic dysregulation. This presentation evaluates new/emerging pharmacological treatments for schizophrenia that have at least one positive phase 2 or phase 3 trial. Novel mechanism agents targeting total symptoms include cannabidiol, D3 antagonist/5-HT1A partial agonist F17464, lumateperone, trace amine-associated receptor-1 (TAAR1) ulotaront, M1/M4 muscarinic agonist xanomeline plus peripheral anticholinergic trospium, and the M4 muscarinic positive allosteric modulator CVL-231. Treatments targeting negative symptoms include the 5-HT2A inverse agonist pimavanserin, and the 5-HT2A/sigma-2 antagonist roluperidone. Agents targeting primarily cognitive dysfunction include the glycine transporter-1 inhibitor BI-425809 and d-amino acid oxidase (DAAO) inhibitor TAK-831. Therapies targeting residual positive symptoms/treatment-resistant schizophrenia include pimavanserin, and the DAAO inhibitor sodium benzoate. Treatments aiming at acute agitation in schizophrenia include the sublingual alpha2 agonist dexmedetomidine. Finally, the recently FDA approved olanzapine+samidorphan combination targets reducing olanzapine's weight gain liability by adding a mu opioid antagonist samidorphan to olanzapine, maintaining olanzapine's efficacy, while the presynaptically acting vesicular monoamine transporter-2 (VMAT-2) inhibitors valbenazine and deutetrabenazine have been FDA approved for the treatment of tardive dyskinesia. Except for the recently FDA-approved agents lumateperone, olanzapine+samidorphan, valbenazine and deutetrabenazine, all remaining trial programs are still ongoing and further positive studies are needed to ensure regulatory approval. Mechanisms of action other than postsynaptic dopamine blockade are urgently needed to broaden therapeutic options but require additional study aiming to improve schizophrenia outcomes for total/positive symptoms with reduced adverse effects, as well as for cognitive symptoms, negative symptoms, and treatment resistance, each of which remain areas of great need in schizophrenia.