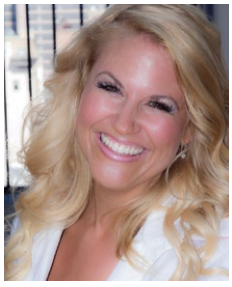
Stephen M. Stahl, MD, PhD



Sabrina Segal, PhD

The third generation of therapeutic innovation and the future of psychopharmacology

The field of psychiatric therapeutics is now experiencing its third generation of progress. No sooner had the pace of innovation in psychiatry and psychopharmacology hit the doldrums a few years ago, following the dwindling of the second generation of progress, than the current third generation of new drug development in psychopharmacology was born.

That is, the first generation of discovery of psychiatric medications in the 1960s and 1970s ushered in the first known psychotropic drugs, such as the tricyclic antidepressants, as well as major and minor tranquilizers, such as chlorpromazine and benzodiazepines, only to fizzle out in the 1980s. By the 1990s, the second generation of innovation in psychopharmacology was in full swing, with the "new" serotonin selective reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors for depression, and the "atypical" antipsychotics for schizophrenia. However, soon after the turn of the century, pessimism for psychiatric therapeutics crept in again, and "big Pharma" abandoned their psychopharmacology programs in favor of other therapeutic areas. Surprisingly, the current "green shoots" of new ideas sprouting in our field today have not come from traditional big Pharma returning to psychiatry, but largely from small, innovative companies. These new entrepreneurial small pharmas and biotechs have found several new therapeutic targets. Furthermore, current innovation in psychopharmacology is increasingly following a paradigm shift away from DSM-5 disorders and instead to domains or symptoms of psychopathology that cut across numerous psychiatric conditions (transdiagnostic model).

So, what are the new therapeutic mechanisms of this current third generation of innovation in

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Disclosures

Dr. Stahl has served as a consultant to AbbVie, Acadia, Alkermes, Allergan, Arbor, Axovant, Axsome, Celgene, ClearView, Concert, EMD Serono, Eisai, Ferring, Impel NeuroPharma, Intra-Cellular, Ironshore, Janssen, Karuna, Lilly, Lundbeck, Merck, Otsuka, Pfizer, Relmada, Sage, Servier, Shire, Sunovion, Takeda, Taliaz, Teva, Tonix, Tris, and Vifor. He is a board member of Genomind, and has served on the speakers' bureaus for Acadia, Lundbeck, Otsuka, Perrigo, Servier, Sunovion, Takeda, Teva, and Vertex. He has received research and/or grant support from Acadia, Avanir, Braeburn, Lilly, Intra-Cellular, Ironshore, International Society for the Study of Women's Sexual Health, Neurocrine, Otsuka, Shire, Sunovion, and TMS NeuroHealth Centers. Dr. Segal reports no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

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Figure 1

Trace amine-associated receptor 1 (TAAR1) agonists reduce presynaptic dopamine synthesis without the need to block postsynaptic dopamine D2 receptors to treat psychosis

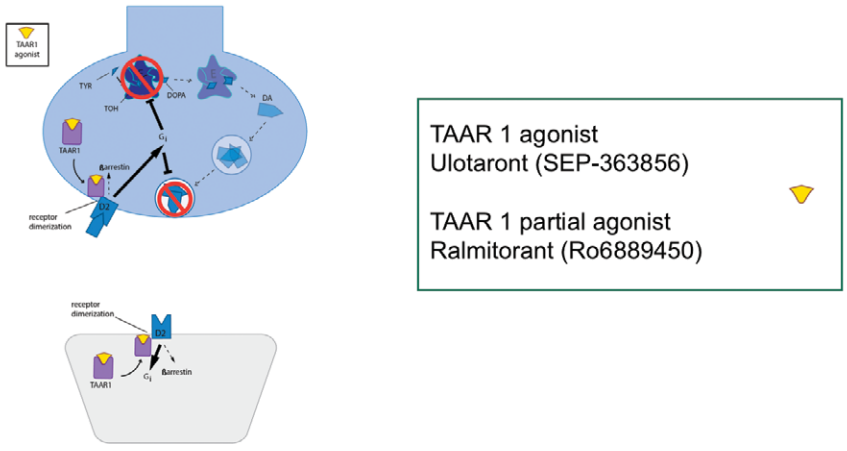

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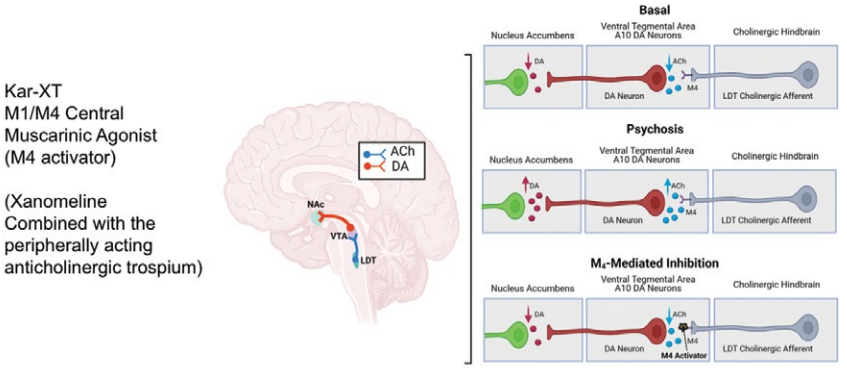
Figure 2

Upstream acetylcholine stimulation of dopamine release reduced by presynaptic M4 activator/agonist without the need to block postsynaptic dopamine D2 receptors to treat psychosis



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psychopharmacology? Not all of these can be discussed here, but 2 examples of new approaches to psychosis deserve special mention because, for the first time in 70 years, they turn away from blocking postsynaptic dopamine D2 receptors to treat psychosis and instead stimulate receptors in other neurotransmitter systems that are linked to dopamine neurons in a network "upstream." That is, trace amine-associated receptor 1 (TAAR1) agonists target the *pre*-synaptic dopamine neuron, where dopamine synthesis and release are too high in psychosis, and cause dopamine

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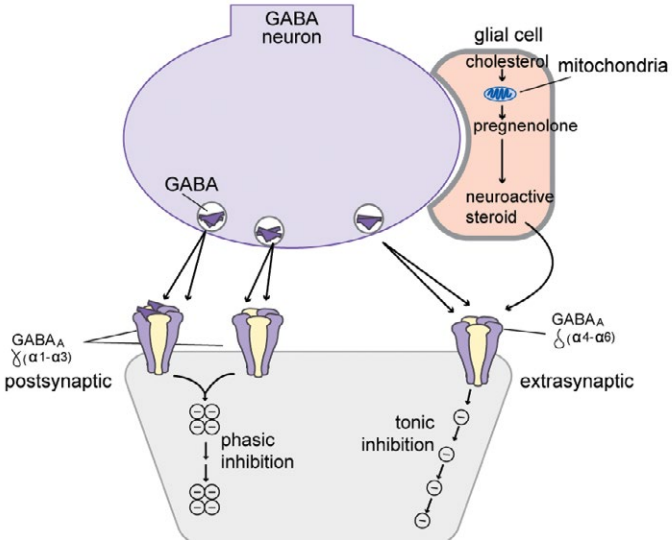
Figure 3

Two types of GABA-A–mediated inhibition: Phasic (benzodiazepine sensitive) and tonic (benzodiazepine insensitive) with both sensitive to neuroactive steroids



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synthesis to be reduced so that blockade of postsynaptic dopamine receptors is no longer necessary (***Table 1*** and ***Figure 1, page 7***).[1] Similarly, muscarinic cholinergic 1 and 4 receptor agonists target excitatory cholinergic neurons upstream, and turn down their stimulation of dopamine neurons, thereby reducing dopamine release so that postsynaptic blockade of dopamine receptors is also not necessary to treat psychosis with this mechanism (***Table 1*** and ***Figure 2, page 7***).[1] A similar mechanism of reducing upstream stimulation of dopamine release by serotonin has led to demonstration of antipsychotic actions of blocking this stimulation at serotonin 2A receptors (***Table 2***), and multiple approaches to enhancing deficient glutamate actions upstream are also under investigation for the treatment of psychosis.[1]

Table 1

Examples of new drug mechanisms in psychopharmacology

Trace amine-associated receptor 1 (TAAR1) agonists for schizophrenia
Cholinergic agonists at central muscarinic M1 and M4 receptors for schizophrenia and psychosis in Alzheimer's dementia
Novel, orally available *N*-methyl-D-aspartate (NMDA) antagonist dextromethorphan combination with either quinidine or bupropion for rapid-onset, treatment-resistant unipolar depression and for agitation in Alzheimer's dementia
Novel, orally available NMDA antagonist esmethadone for rapid-onset, potentially treatment-resistant depression
Neuroactive steroids as novel GABA-A positive allosteric modulators for rapid-onset antidepressant action in unipolar depression and postpartum depression

Table 2

Examples of novel potential indications for approved drugs in psychopharmacology

Lumateperone for bipolar depression and augmentation of SSRIs/SNRIs in unipolar depression
Cariprazine for augmentation of SSRIs/SNRIs in unipolar major depressive disorder
Brexpiprazole for agitation in Alzheimer's dementia and in posttraumatic stress disorder
Pimavanserin for negative symptoms of schizophrenia and for dementia-related psychosis

SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors

Another major area of innovation in psychopharmacology worthy of emphasis is the rapid induction of neurogenesis that is associated with rapid reduction in the symptoms of depression, even when many conventional treatments have failed. Blockade of *N*-methyl-D-aspartate (NMDA) glutamate receptors is associated with rapid neurogenesis

continued on page 25

that may hypothetically drive rapid recovery from depression.[1] Proof of this concept was first shown with intravenous ketamine, and then intranasal esketamine, and now the oral NMDA antagonists dextromethorphan (combined with either bupropion or quinidine) and esmethadone (***Table 1, page 8***).[1] Interestingly, this same mechanism may lead to a novel treatment of agitation in Alzheimer's dementia as well.[1]

Yet another mechanism of potentially rapid onset antidepressant action is that of the novel agents known as neuroactive steroids that have a novel action at gamma aminobutyric acid A (GABA-A) receptors that are not sensitive to benzodiazepines (as well as those that are) (***Table 1*** and ***Figure 3, page 8***).[1] Finally, psychedelic drugs that target serotonin receptors such as psilocybin and 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") seem to also have rapid onset of both neurogenesis and antidepressant action.[1] The list of innovations goes on and on, and also includes many novel potential indications for already approved agents (***Table 2, page 8***). Hopefully, these tables listing new therapeutic targets for psychiatric disorders as well as the discussion here provide the reader with a glimpse into the excitement and innovations afoot in this third generation of drug development in psychiatry.

The future of psychopharmacology is clearly going to be amazing.

This third generation of innovation in psychopharmacology focuses on new therapeutic mechanisms

Reference

1. Stahl SM. Stahl's Essential Psychopharmacology. 5th ed. Cambridge University Press; 2021.