

System MOA Single	System MOA Additional	Mechanism Of Action
Serotonergic		5 Hydroxytryptamine 1A receptor agonist 5 Hydroxytryptamine 1A receptor agonist 5 Hydroxytryptamine 1A receptor agonist; Trace amine associated receptor 1 agonist; 5 Hydroxytryptamine uptake inhibitor; 5 Hydroxytryptamine 1A receptor agonist 5 Hydroxytryptamine uptake inhibitor; 5 Hydroxytryptamine partial 1A receptor agonist 5 Hydroxytryptamine 1A receptor agonist; 5 Hydroxytryptamine 7 receptor antagonist; 5 Hydroxytryptamine 1B receptor agonist; 5 Hydroxytryptamine uptake inhibitor; 5 Hydroxytryptamine 1D receptor antagonist; 5 Hydroxytryptamine 3 receptor antagonist 5 Hydroxytryptamine 2A/2C receptor antagonist 5 Hydroxytryptamine 1A receptor antagonist; 5 Hydroxytryptamine 2A receptor antagonist; 5 Hydroxytryptamine uptake inhibitor
	Adrenergic	antagonist/inverse agonist of: H1, 5-HT1D, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3, 5-HT6, 5-HT7, α 1-adrenergic, and α 2-adrenergic receptors, and also inhibits Alpha 2 adrenoreceptor antagonist; 5 Hydroxytryptamine 2A receptor antagonist; 5 Hydroxytryptamine 2C receptor antagonist

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Dopaminergic

5 Hydroxytryptamine 2A/3A receptor antagonist

Alpha 2 adrenergic auto- and hetero-receptors

5 Hydroxytryptamine 2A receptor antagonist;

5 Hydroxytryptamine 2C receptor antagonist;

5 Hydroxytryptamine 6 receptor antagonist;

Dopamine D1 receptor antagonist;

Dopamine D2 receptor antagonist;

5 Hydroxytryptamine uptake inhibitor

5 Hydroxytryptamine 2A receptor antagonist; Dopamine D2 receptor antagonist

5 Hydroxytryptamine 2A receptor antagonist; 5 Hydroxytryptamine uptake inhibitor; Dopamine D2 receptor agonist; Dopamine receptor antagonist

5 Hydroxytryptamine 1A receptor agonist; 5 Hydroxytryptamine 2A receptor antagonist; Dopamine D4 receptor agonist

Dopamine D2 receptor agonist; 5 Hydroxytryptamine 1A receptor agonist; 5 Hydroxytryptamine 2A receptor antagonist

Dopamine D2 receptor agonist; 5 Hydroxytryptamine 1A receptor agonist; Dopamine D3 receptor agonist; Dopamine D4 receptor agonist; 5 Hydroxytryptamine 6 receptor antagonist; 5 Hydroxytryptamine 7 receptor antagonist; 5 Hydroxytryptamine 2B receptor antagonist; 5 Dopamine D2 receptor agonist; Dopamine D3 receptor agonist; 5 Hydroxytryptamine 1A receptor agonist; 5 Hydroxytryptamine 2A receptor antagonist

		Dopamine D2 receptor antagonist; 5 Hydroxytryptamine 7 receptor antagonist; 5 Hydroxytryptamine 1A receptor antagonist; 5 Hydroxytryptamine 2A receptor antagonist 5-hydroxytryptophan Decarboxylase inhibitor
	Dopaminergic Adrenergic	5 Hydroxytryptamine 2A receptor antagonist; Dopamine D2 receptor antagonist; Alpha 1 adrenoreceptor antagonist
	Dopaminergic Opioidergic	5 Hydroxytryptamine 2A receptor antagonist; Dopamine D1 receptor antagonist; Opioid mu agonist
	Histaminergic Adrenergic	5 Hydroxytryptamine 2A receptor antagonist; Histamine H1 receptor antagonist; Alpha 1 adrenoreceptor antagonist
	Dopaminergic Adrenergic Muscarinic Histaminergic	5 Hydroxytryptamine 2A receptor antagonist; 5 Hydroxytryptamine 2C receptor antagonist; 5 Hydroxytryptamine 6 receptor antagonist; Dopamine D1 receptor antagonist; Dopamine D2 receptor antagonist; Dopamine D3 receptor antagonist; Dopamine D4 receptor antagonist; Alpha 1 adrenoreceptor antagonist; 5 Hydroxytryptamine 3 receptor antagonist; Histamine H1 receptor antagonist; Muscarinic M1 receptor antagonist; Muscarinic M2 receptor antagonist; Muscarinic M3 receptor antagonist; Muscarinic M4 receptor antagonist; 5 Hydroxytryptamine uptake inhibitor

		5 Hydroxytryptamine 2A receptor antagonist; 5 Hydroxytryptamine 2C receptor antagonist; 5 Hydroxytryptamine 6 receptor antagonist; Dopamine D1 receptor antagonist; Dopamine D2 receptor antagonist; Dopamine D3 receptor antagonist; Dopamine D4 receptor antagonist; Alpha 1 adrenoreceptor antagonist; Muscarinic M4 receptor antagonist; Histamine H1 receptor antagonist; 5 Hydroxytryptamine 3 receptor antagonist
	endoannabinoid	Cannabinoid CB1 receptor agonist; 5 Hydroxytryptamine 1A receptor agonist
Cholinergic		Muscarinic receptor antagonist; Muscarinic M1 receptor antagonist; Muscarinic M2 receptor antagonist; Muscarinic M3 receptor antagonist; Muscarinic M4 receptor antagonist
	intracellular signalling cascade	Muscarinic M1 receptor agonist; Muscarinic M2 receptor antagonist; Sigma 1 receptor agonist
Glutamatergic		NMDA receptor antagonist
		NMDA receptor antagonist
		NMDA receptor antagonist
		NMDA receptor antagonist
		NMDA receptor antagonist
		S-ketamine: AMPA receptor agonist; R-ketamine: NMDA receptor antagonist
		NMDA receptor antagonist pro-drug
		glutamate ionotropic receptor NMDA type subunit 1 (GRIN1)
		NMDAR antagonist (ketamine 'analog')
		NMDA receptor antagonist, immediate release
		NMDAR antagonist (abuse-deterrent oral ketamine formulation)
		NMDA receptor antagonist

		NMDA receptor antagonist
		NMDA receptor antagonist, transmucosal NMDA receptor antagonist
		NMDA receptor antagonist (weak)
		NMDA receptor, subunit 2B antagonist
		NMDA receptor, subunit 2B antagonist(negative allosteric modulator (NAM))
		NMDA receptor, subunit 2B antagonist
		NMDA modulator
		NMDA partial co-agonist
		NMDA receptor positive allosteric modulator (PAM) Glycine transporter 1 inhibitor NMDA receptor antagonist; AMPA receptor agonist Indirect inhibitor of NMDA at Glycine site NMDA receptor antagonist
		Adenosine A2a receptor antagonist
GLutamatergic	intracellular signalling cascade	weak NMDA receptor antagonist; Sigma 1 receptor agonist
Glutamatergic	Dopaminergic serotonergic	Dopamine D2 receptor antagonist; 5 Hydroxytryptamine 7 receptor antagonist; 5 Hydroxytryptamine 1A receptor antagonist; 5 Hydroxytryptamine 2A receptor antagonist; Glycine NMDA associated
Glutamatergic	Noradrenergic Dopaminergic intracellular signalling cascade	NMDA receptor antagonist (weak); NDRI sigma-1 agonist

Gabaergic

Benzodiazepine receptor agonist

Benzodiazepine receptor agonist

GABA-A receptor agonist

GABA A receptor agonist (Non-benzodiazepine hypnotic)

GABA A receptor agonist

GABA-A receptor alpha1, 2, 3, 5 subunit agonist

GABA-A receptor alpha1, 2, 3, 5 subunit agonist

GABA A receptor positive allosteric modulator (PAM)

GABA A receptor positive allosteric modulator (PAM)

GABA A receptor positive allosteric modulator (PAM)

intracellular signalling cascade

GABA A receptor negative allosteric modulator (NAM); Calcium channel antagonist

GABA receptor agonist; Chloride channel agonist; Potassium channel agonist

GABA A receptor b-2/3 agonist; Chloride channel agonist; Translocator protein agonist

serotonergic

Benzodiazepine receptor agonist; Tricyclic antidepressant; Serotonin and norepinephrine reuptake inhibitor

Gabaergic	serotonergic noradrenergic	Tricyclic antidepressant; Serotonin and norepinephrine reuptake inhibitor; Benzodiazepine receptor agonist
Hormone / neurosteroid		Glucocorticoid antagonist
Hormone / neurosteroid		Androgen receptor agonist
Hormone / neurosteroid		Orexin-2 receptor antagonist
Hormone / neurosteroid		Orexin-1 receptor antagonist
Hormone / neurosteroid		a vomeropherin, which may inhibit CRH
Hormone / neurosteroid		Vasopressin 1a antagonist
hormone / neurosteroid		Vasopressin 1B antagonist
Hormone / neurosteroid		Melatonin 1 receptor agonist; Melatonin 2 receptor agonist
Hormone / neurosteroid		11 Beta hydroxysteroid dehydrogenase inhibitor
Hormone / neurosteroid		Prostaglandin E2 receptor antagonist; Reducing agent
Hormones / neurosteroid		Corticotropin releasing factor 1 receptor antagonist
Hormone / neurosteroid:	Serotonergic	Melatonin 1/2 receptor agonist; 5 Hydroxytryptamine 2C receptor antagonist
Intracellular signalling cascade		Interleukin 6 antagonist
		Microtubule stabilizer
		Mitogen-activated protein kinase 14 inhibitor

intracellular signalling cascade Immune pathway	opioidergic	mTORC1 kinase stimulator
		Omega 3 fatty acid stimulant; Caspase inhibitor
		Phosphodiesterase 4 inhibitor negative allosteric modulator (NAM)
		Phosphodiesterase 4B allosteric inhibitor
		Protein kinase C epsilon stimulant
		HMGCoA reductase inhibitor
		Carnitine O-acetyltransferase stimulant
		Catechol O methyltransferase inhibitor
		Sodium channel antagonist
		TrkB tyrosine kinase stimulant
		TRPC4 antagonist; TRPC5 antagonist
		Tyrosine kinase inhibitor (TKI)
		synthetic peptide targeting MAP kinase / ERK signaling pathway and associated cellular functions Fibroblast growth factor 9 aptamer antagonist
		DNA-methylation via DNA methyltransferase 3A (DNMT3A)
		activates transient receptor potential ion channel TRPC6, which increases Na/K entry into cell and decreases monoamine reuptake
		sigma 1 agonist
		Muscarinic M2 antagonist
		Muscarinic M3 antagonist
		TrkB tyrosine kinase stimulant; Opioid kappa receptor antagonist
		Platelet-derived growth factor receptor kinase inhibitor; C-kit inhibitor; FGF receptor 3 tyrosine kinase inhibitor; LYN tyrosine kinase inhibitor; Fyn tyrosine kinase inhibitor; Colony stimulating factor 1 receptor antagonist

Immune pathway

Interleukin 6 antagonist

Notes: Multiple categories of novel MOAs have been removed from this presentation. These
Workshop Interestketamine / esketamine / R-ketamineOther NMDA-R antagonists GABA mc

Source: Adapted by Cohen Veterans Bioscience from Informa February 2021

Generic Drug Name	Highest Status Reached in Major Depressive Disorder (MDD/TRD)	Highest Status Reached	Trial Count (all indications)
NLX-101	Preclinical	Preclinical	1
SKL-PSY	Preclinical	Preclinical	2
SEP-363856	Phase I Clinical Trial	Phase I Clinical Trial	17
hypidone hydrochloride	Phase II Clinical Trial	Phase II Clinical Trial	6
vilazodone	Launched (MDD)	Launched (MDD)	50
vortioxetine	Launched (MDD)	Launched (MDD)	125
pimvanserin tartrate	Phase III Clinical Trial	Launched (Psychosis in Parkinson's)	49
MIN-117	Phase II Clinical Trial (MDD; development stopped for lack of efficacy)	Phase II Clinical Trial	5
mianserin	Launched (MDD - ex-US)	Launched (MDD - ex-US)	14
setiptiline	Launched (MDD - ex-US)	Launched (MDD - ex-US)	1

mirtazipine	Launched (MDD)	Launched (MDD)	286
fluoxetine 20mg + olanzapine 5mg and olanzapine 10mg + fluoxetine 20mg	Launched (TRD)	Launched (TRD / BP1 depression)	0
iloperidone	Preclinical	Phase III Clinical Trial	36
lumateperone tosylate	Phase III Clinical Trial	Phase III Clinical Trial	21
flibanserin	Phase III Clinical trial (discontinued for lack of efficacy in MDD)	Launched (acquired, generalized HSDD)	28
aripiprazole	Launched (MDD - adjunctive)	Launched (MDD - adjunctive, Schizophrenia, Bipolar I, Irritability in Autism, Tourette's)	9
brilaroxazine	Phase I Clinical Trial	Phase II Clinical Trial	8
brexpiprazole	Launched (MDD - adjunctive)	Launched (MDD - adjunctive, Schizophrenia)	110

lurasidone hydrochloride	Phase III Clinical Trial	Launched (schizophrenia; Bipolar Disorder I)	89
EVX-101	Phase I Clinical Trial	Phase I Clinical Trial	1
risperidone	Phase III Clinical Trial	Launched (Schizophrenia, Bipolar, Irritability in Autism)	809
ITI-333	Preclinical	Phase I Clinical Trial	1
cyclobenzaprine	Preclinical	Phase III Clinical Trial	25
fluoxetine + olanzapine	Launched (TRD)	Launched (TRD, Bipolar)	19

olanzapine	Launched (TRD: USA only)	Launched (TRD, Schizophrenia, Bipolar Disorder)	941
MP-20X	Preclinical	Preclinical	0
scopolamine (intranasal)	Phase I Clinical Trial	Phase III	1
ANAVEX-1-41	Preclinical	Preclinical	0
ketamine, extended release	Phase II Clinical Trial	Phase II Clinical Trial	4
sublingual ketamine	Patent	Phase II Clinical Trial	11
ketamine	Phase III Clinical Trial	Phase III Clinical Trial	3
ketamine	Preclinical	Preclinical	3
ketamine, transdermal	Phase II Clinical Trial	Phase II Clinical Trial	1
ketamine	Preclinical	Preclinical	0
ketamine	Phase III Clinical Trial	Phase II Clinical Trial	4
BHV-5000	Preclinical	Preclinical	4
ketamine	Preclinical	Preclinical	0
ELE-Ket+	Preclinical	Preclinical	1
NX-100	Preclinical	Preclinical	0
NX-101	Preclinical	Preclinical	0
esketamine	Phase II Clinical Trial	Phase II Clinical Trial	3

esketamine	Launched (TRD)	Launched (TRD; MDSI)	47
R-ketamine	Preclinical	Phase I Clinical Trial	1
dextromethadone	Phase III Clinical Trial	Phase III Clinical Trial	11
amantadine	Phase I Clinical Trial	Launched (influenza A; parkinsonism)	14
CERC-301	Phase II Clinical Trial	Phase II Clinical Trial	8
MIJ-821	Phase II Clinical Trial	Phase II Clinical Trial	3
NP-10679	Preclinical	Phase I Clinical Trial	3
CLE-100	Phase II Clinical Trial	Phase II Clinical Trial	1
AGN-241751	Phase II Clinical Trial	Phase II Clinical Trial	2
SAGE-718	Preclinical	Phase I Clinical Trial	9
SNG-12	Phase II Clinical Trial	Phase II Clinical Trial	2
XW-10508	Preclinical	Preclinical	0
AV-101	Preclinical	Phase II Clinical Trial	8
istradefylline	Preclinical (suspended)	Phase II Clinical Trial	49
deuterated dextromethorphan + quinidine	Phase II Clinical Trial	Phase II Clinical Trial	17
D-cycloserine + lurasidone	Phase III Clinical Trial	Phase III Clinical Trial	6
bupropion + dextromethorphan	Phase III Clinical Trial	Phase III Clinical Trial	15

cloxazolam	Launched (ex. USA)	Launched (anxiety - Ex-US)	1
alprazolam	Launched (depression - Ex-US)	Launched (Anxiety disorders, Panic Disorders)	66
zuranolone	Phase III Clinical Trial	Phase III Clinical Trial	17
eszopiclone	Phase III Clinical Trial	Phase III Clinical Trial	84
brexanolone	Preclinical	Launched (Post-partum depression)	13
pinazepam	Launched (ex. USA)	Launched	0
metaclazepam	Launched (ex. USA)	Launched	0
PRAX-114	Phase II Clinical Trial	Phase II Clinical Trial	5
captisol-enabled ganaxolone	Phase II Clinical Trial	Phase II Clinical Trial	4
ganaxolone	Phase II Clinical Trial	Phase II Clinical Trial	25
LCGA-17	Preclinical	Preclinical	0
rilmazafone	Launched (MDD - Japan)	Launched (MDD - Japan)	1
deuterated etifoxine, GABA Therapeutics	Preclinical	Phase I Clinical Trial	1
amitriptyline HCl + chlordiazepoxide, A. N. Pharmacia Laboratories	Launched (depression with anxiety)	Launched	0
escitalopram + clonazepam	Launched (MDD)	Launched (MDD)	

imipramine hydrochloride + diazepam	Launched (MDD)	Launched (MDD)	0
PT-150	Phase II Clinical Trial	Phase II Clinical Trial	4
prasterone	Launched (MDD - Italy)	Launched (MDD, Hormonal disorders)	0
JNJ-42847922	Phase III Clinical Trial	Phase III Clinical Trial	30
JNJ-61393215	Phase II Clinical Trial	Phase II Clinical Trial	7
PH-10	Phase II Clinical Trial	Phase II Clinical Trial	5
SRX-246	Preclinical	Phase I Clinical Trial	8
TS-121	Phase II Clinical Trial	Phase II Clinical Trial	2
tasimelteon	Phase I Clinical Trial (MDD; Discontinued for lack of efficacy)	Launched (non-24Hr Sleep-wake Disorder)	31
Xanamem	Preclinical	Phase II Clinical Trial (Discontinued)	9
crisdesalazine	Preclinical	Phase I Clinical Trial	2
tildacerfont	Preclinical (Discontinued)	Preclinical	5
agomelatine	Launched (MDD - Ex-US)	Launched (MDD- Ex-US)	154
sirukumab	Preclinical (Discontinued)	Phase II Clinical Trial	21
MAP-4343	Phase II Clinical Trial	Phase II Clinical Trial	3
losmapimod	Phase II Clinical Trial	Phase II Clinical Trial	30

NV-5138	Phase I Clinical Trial	Phase I Clinical Trial	2
ethyl icosapentate, Amarin	Phase III Clinical Trial	Phase III Clinical Trial	36
BPN-14770	Preclinical	Preclinical	8
TDP-101	Preclinical	Preclinical	0
bryostatin, Neurotrope	Preclinical	Preclinical	8
rosuvastatin calcium	Phase II Clinical Trial	Phase II Clinical Trial	918
acetyl L-carnitine	Launched (depression, unspecified -ex. USA)	Launched (Alzheimer's; Cancer; Depression)	61
CERC-406	Preclinical	Preclinical	0
evenamide	Preclinical	Preclinical	9
TrkB agonist	Preclinical	Preclinical	0
BI-1358894	Phase II Clinical Trial	Phase II Clinical Trial	13
NNI-351	Preclinical	Preclinical	0
PepElk	Preclinical	Preclinical	0
FGF-9 aptamer	Preclinical	Preclinical	0
SLS-004	Preclinical	Preclinical	0
Xantol	Preclinical	Preclinical	0
blarcamesine hydrochloride	Preclinical	Phase III Clinical Trial	15
S013-1304	Preclinical	Preclinical	0
masitinib	Phase II Clinical Trial	Phase II Clinical Trial	60

sirukumab

Phase II Clinical Trial

Phase II Clinical Trial
(Discontinued for safety)

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