Next Generation Antidepressants

Moving Beyond Monoamines to Discover Novel Treatment Strategies for Mood Disorders
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As the World Health Organization estimates that depression will become the second leading cause of death by the year 2020 – due primarily to complications arising from stress and the cardiovascular system – the need to develop novel and more effective treatment strategies for patients suffering with mood disorders has never been more paramount. Current treatment options for depressed patients include a variety of molecules designed to exclusively elevate central nervous system levels of monoamines such as serotonin (5-HT). These classes include the monoamine oxidase inhibitors and tricyclics and are exemplified by the selective serotonin reuptake inhibitors (SSRIs) and the dual serotonin/norepinephrine reuptake inhibitors (SNRIs). While these medicines are moderately effective in some patient populations, there are still considerable limitations associated with all commercially available antidepressants. These drawbacks include, but are not limited to, delayed onset of efficacy, treatment resistance in many patients, and deleterious side effects such as emesis and sexual dysfunction. The focus of this book is to review the current landscape and state of the field for depression research with an eye towards shedding light on where the future of mood disorders research is headed in terms of novel therapeutic targets, preclinical model development, exploring depression endophenotypes, and medicinal chemistry strategies. Undoubtedly all of these disciplines, as well as others including genetics and translational medicine approaches, will need to successfully collaborate to help build a better understanding of disease etiology, patient stratification, and treatment. As depression research has evolved over the past 50 years, the next decade will be instrumental in facilitating a move beyond our current understanding and pharmacological treatment options, and strive to discover and develop more personalized and effective treatment options for the millions of patients suffering from chronic and debilitating mood disorders.

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Abbreviations

5HIAA, 5-hydroxy-indole-acetic acid
ACTH, adrenocorticotropic hormone
BBB, blood–brain barrier
BD, bipolar disorder
BDI, Beck Depression Inventory
BDNF, brain-derived neurotrophic factor
BNST, bed nucleus of the stria terminalis
BOLD, blood oxygen level-dependent
CANTAB, Cambridge Neuropsychological Test Automated Battery
CBF, cerebral blood flow
CBV, cerebral blood volume
CNV, copy-number variation
CRF, corticotropin-releasing factor
CSF, cerebrospinal fluid
DA, dopamine
DAT, dopamine transporter
DRN, dorsal raphe nucleus
DST, dexamethasone suppression test
ECT, electro-convulsive therapy
ERP, event-related potential
FDG, fluorine-18-labeled deoxyglucose
FLAIR, fluid attenuated inverse recovery
fMRI, functional magnetic resonance imaging
FST, forced swim test
GWAS, genomewide association study
HPA, hypothalamic–pituitary–adrenal
IAT, Implicit Association Test
LC, locus coerules
MAOI, monoamine oxidase inhibitor
MDD, major depressive disorder
MED, minimal effective dose
MTD, maximal tolerated dose
MRN, median raphe nucleus
MRS, magnetic resonance spectroscopy
MTHF, L-5-methyl-tetrahydrofolate
NE, norepinephrine
NET, norepinephrine transporter
NK, neurokinin
PET, positron emission tomography
PFC, prefrontal cortex
phMRI, pharmacological MRI
POC, proof-of-concept
List of abbreviations

SERT, serotonin transporter
SNP, single nucleotide polymorphism
SNRI, serotonin/norepinephrine reuptake inhibitor
SP, substance P
SSRI, selective serotonin reuptake inhibitor
STAR*D, Sequenced Treatment Alternatives to Relieve Depression study
SXR, steroid and xenobiotic receptor
T3, triiodothyronine
TCA, tricyclic antidepressant
TCI, Temperament and Character Inventory
TST, tail suspension test
vACC, ventral anterior cingulate cortex
VTA, ventral tegmental area
WCST, Wisconsin Card Sorting Test
WGTA, Wisconsin General Testing Apparatus
WMH, white matter hyperintensities