CNS SPECTRUMS

CME Review Article

Modulating the Serotonin System in the Treatment of Major Depressive Disorder

This activity is sponsored by the Neuroscience Education Institute

https://doi.org/10.1017/S1092852914000613 Published online by Cambridge University Press

CME Information

Accreditation and Credit Designation Statements

The Neuroscience Education Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Neuroscience Education Institute designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Target Audience

This activity has been developed for prescribers specializing in psychiatry. There are no prerequisites. All other health care providers interested in psychopharmacology are welcome for advanced study, especially primary care physicians, nurse practitioners, psychologists, and pharmacists.

Statement of Need

Major depressive disorder (MDD) is a serious and often crippling psychiatric illness with a high risk of relapse and treatment resistance. MDD affects as many as 16% of the US population and has been estimated by the World Health Organization (WHO) as one of the leading causes of years lived with disability. Many patients with MDD do not respond to currently available treatments and suffer through recurring depressive episodes.

The timely detection, diagnosis, and comprehensive treatment of MDD have been shown to increase the probability of positive clinical outcomes. To help improve outcomes for patients with MDD, quality improvement efforts need to provide education regarding (1) best practices for management of residual symptoms of depression, (2) best practices for avoidance and/or management of the most troubling side effects associated with antidepressant treatment, and (3) best practices for addressing treatment-resistant depression.

Learning Objective

After completing this activity, participants should be better able to discuss the theory of modulation of receptor activity or the blockade of the reuptake of multiple neurotransmitter systems for the future treatment of MDD.

Date of Release/Expiration

Released: December, 2014
CME credit expires: November, 2017

Sponsor

This activity is sponsored by the Neuroscience Education Institute.

Acknowledgment of Financial Support

This activity is supported by an educational grant from Takeda Pharmaceuticals International, Inc.

Instructions

You are advised to review this activity from beginning to end, evaluate the content presented, and then complete the posttest and activity evaluation. The estimated time for completion of this activity is 60 minutes.

To receive your certificate of CME credit or participation, complete the posttest and activity evaluation, available only online at www.neiglobal.com/CME under "CNS Spectrums". If a score of 70% or more is achieved, you will be able to immediately print your certificate. There is no posttest fee nor fee for CME credits for this activity. If you have questions, please call 888-535-5600, or email customerservice@neiglobal.com.

Peer Review

These materials have been peer reviewed to ensure the scientific accuracy and medical relevance of information presented and its independence from commercial bias. NEI takes responsibility for the content, quality, and scientific integrity of this CME activity.

Disclosures

It is the policy of the Neuroscience Education Institute to ensure balance, independence, objectivity, and scientific rigor in all its educational activities. Therefore, all individuals in a position to influence or control content are required to disclose any financial relationships. Although potential conflicts of interest are identified and resolved prior to the activity being presented, it remains for the participant to determine whether outside interests reflect a possible bias in either the exposition or the conclusions presented.

Disclosed financial relationships with conflicts of interest have been reviewed by the Neuroscience Education Institute CME Advisory Board Chair and resolved.

Author

Debbi Ann Morrissette, PhD, is an adjunct professor of biological sciences at Palomar College in San Marcos, CA,

and at California State University in San Marcos, CA, and a medical writer at the Neuroscience Education Institute in Carlsbad, CA. Dr. Morrissette has no financial relationships to disclose.

No writing assistance was utilized in the production of this article.

Content Editor

Stephen M. Stahl, MD, PhD, is an adjunct professor of psychiatry at the University of California, San Diego School of Medicine, an honorary visiting senior fellow at the University of Cambridge in the UK, and Director of Psychopharmacology for the California Department of State Hospitals. Dr. Stahl receives research support from Assurex, EnVivo, Lilly, Janssen, JayMac, Jazz, Lundbeck, Mylan, Neuronetics, Novartis, Otsuka America, Pamlab, Pfizer, Roche, Shire, Sunovion, Takeda, Teva, and Valeant; is a consultant/advisor to AstraZeneca, Avanir, BioMarin, EnVivo, Forest, Jazz, Lundbeck, Neuronetics, Noveida, Orexigen, Otsuka America, Pamlab, Servier, Shire, Sunovion, Taisho, Takeda, and Trius; is on the speakers bureaus of AstraZeneca, Janssen, Otsuka America, Sunovion, and Takeda; and is a board member at Genomind and RCT Logic.

CNS Spectrums Peer Review

All CME articles are peer reviewed in accordance with the strict standards of *CNS Spectrums* and in accordance with requirements and recommendations of the International Committee of Medical Journal Editors. The editorial policies of the journal *CNS Spectrums* and peer review of all articles that appear in the journal is managed independently by Cambridge University Press and no financial relationship exists between the CME provider and Cambridge for this service.

Additional Peer Reviewer

Ronnie Gorman Swift, MD, is a professor in and associate chairman of the department of psychiatry and behavioral sciences at New York Medical College in Valhalla, NY, and the chief of psychiatry and associate medical director at Metropolitan Hospital Center in New York, NY. Dr. Swift has no financial relationships to disclose.

Program Development

Sheri Mills is the director of program development at the Neuroscience Education Institute in Carlsbad, CA. She has no financial relationships to disclose.

Steve Smith is the president and chief executive officer at the Neuroscience Education Institute in Carlsbad, CA. He has no financial relationships to disclose.

Disclosure of Off-Label Use

This educational activity may include discussion of unlabeled and/or investigational uses of agents that are not currently labeled for such use by the FDA. Please consult the product prescribing information for full disclosure of labeled uses.

Disclaimer

Participants have an implied responsibility to use the newly acquired information from this activity to enhance patient outcomes and their own professional development. The information presented in this educational activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this educational activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities. Primary references and full prescribing information should be consulted.

Cultural and Linguistic Competency

A variety of resources addressing cultural and linguistic competency can be found at this link: www.neiglobal.com/go/cmeregs

https://doi.org/10.1017/S1092852914000613 Published online by Cambridge University Press

CNS Spectrums, page 4 of 15. © Cambridge University Press 2014
doi:10.1017/S1092852914000613

CME REVIEW ARTICLE

Modulating the serotonin system in the treatment of major depressive disorder

Debbi Ann Morrissette[1,2,3,*] *and Stephen M. Stahl*[1,4,5]

[1] Neuroscience Education Institute, Carlsbad, CA, USA
[2] Department of Biology, Palomar College, San Marcos, CA, USA
[3] Department of Biology, California State University, San Marcos, CA, USA
[4] Department of Psychiatry, University of California, San Diego, USA
[5] Department of Psychiatry, University of Cambridge, UK

Learning Objective: Discuss the theory of modulation of receptor activity or the blockade of the reuptake of multiple neurotransmitter systems for the future treatment of MDD.

Major depressive disorder (MDD) is a serious and often crippling psychiatric illness with a high risk of relapse and treatment resistance. In this article, we discuss the role of the serotonergic system in MDD including our current understanding of how various serotonin (5HT) receptors modulate monoamine neurotransmission and behavior. We also discuss how pharmacologic interventions, including novel and existing antidepressants and atypical antipsychotics, may be utilized to adjust serotonergic neurotransmission and provide more effective treatments for patients with MDD.

Received 2 October 2014; Accepted 11 October 2014

Key words: atypical antipsychotic, serotonin, SERT, vortioxetine, vilazodone.

Introduction

Major depressive disorder (MDD) affects as much as 16% of the U.S. population and has been estimated by the World Health Organization (WHO) to be one of the leading causes of years lived with disability.[1] Many patients with MDD do not respond to currently available treatments and suffer through recurring depressive episodes.[2] The monoamine hypothesis of depression, which posits that depression results from a deficiency in serotonin (5HT), norepinephrine (NE), and dopamine (DA), has been the mainstay of antidepressant treatments including selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).[3] Here we provide a review of the serotonergic system and our understanding of its role in major depressive disorder. We also discuss how modulation of 5HT neurotransmission via pharmacological agents that act at various 5HT receptors and reuptake transporters may provide novel antidepressant treatments.

Serotonin Circuits

Serotonin circuits arise from discrete brainstem nuclei, including the dorsal and medial raphe nuclei. These circuits project to a wide range of cortical and subcortical brain areas: prefrontal cortex (PFC), hippocampus, amygdala, thalamus, hypothalamus, striatum, nucleus accumbens, basal forebrain, cerebellum, and spinal cord (Figure 1).[4] Serotonergic neurons directly and indirectly influence virtually all other neurotransmitter systems–DA, NE, glutamate (Glu), acetylcholine (ACh), histamine (HA), and gamma-aminobutyric acid (GABA)–as well as self-modulation of the 5HT system. Thus, it is not surprising that the 5HT system is thought to regulate a variety of behaviors including mood, sleep, and appetite, and that dysregulation of the 5HT system has been implicated in many psychiatric disorders, including major depressive disorder (MDD).[4,5]

Serotonin Receptors

There are 7 families of 5HT receptors, with at least 14 subtypes (Table 1). Activation of each of the 5HT receptors leads to G-protein–coupled cascades, with the exception of the 5HT3 receptor, which is a ligand-gated ion channel.[6] Our discussion will focus on the potential roles of 5HT1A, 5HT1B, 5HT1D, 5HT2A, 5HT2C, 5HT3, 5HT4, 5HT6, and 5HT7 receptors in depression, as less is currently known about how 5HT1E, 5HT1F, 5HT2B, and 5HT5 may be involved in the neurobiology and treatment of MDD.

* Address for correspondence: (Email: dmorrissette@neiglobal.com)

This activity is supported by an educational grant from Takeda Pharmaceuticals International, Inc.

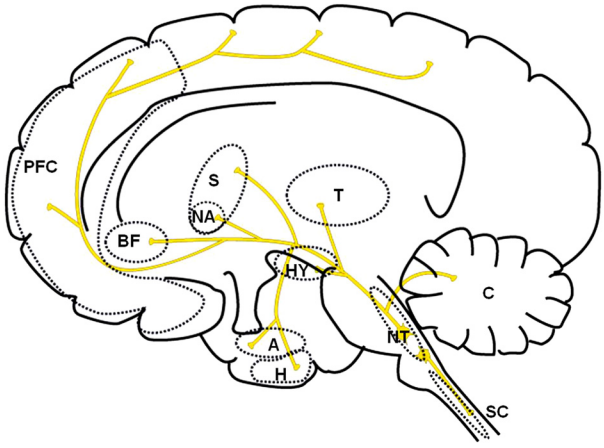

FIGURE 1. Serotonin circuits throughout the brain. Serotonin has both ascending and descending projections. Ascending serotonergic projections originate in the brainstem neurotransmitter centers (NT) and extend to various brain regions, including the prefrontal cortex (PFC), basal forebrain (BF), nucleus accumbens (NA), striatum (S), thalamus (T), hypothalamus (HY), amygdala (A), hippocampus (H), and cerebellum (C), where they regulate mood, sleep, anxiety, appetite, and many other behaviors. Descending serotonergic projections extend down the brainstem and through the spinal cord (SC) where they regulate pain.

5HT1A

Serotonin 5HT1A receptors are located postsynaptically in the hippocampus, septum, amygdala, and corticolimbic areas, where they regulate release of other neurotransmitters. Serotonin 5HT1A postsynaptic heteroreceptors control release of ACh in the septum, Glu neurotransmission in the PFC, and DA signaling in the ventral tegmental area (VTA).[7–9] Additionally, 5HT1A receptors exist as presynaptic somatodendritic autoreceptors on 5HT neurons in the raphe nuclei, where they inhibit 5HT neurotransmission (Figure 2).[7] Not only are 5HT1A receptors associated with depression, but modulation of signaling through both pre- and postsynaptic 5HT1A receptors may also ameliorate antipsychotic-induced extrapyramidal symptoms (EPS) by increasing nigrostriatal DA neurotransmission.[4,9] Numerous psychotropic agents possess 5HT1A binding affinity, including the antidepressants vilazodone and vortioxetine, the atypical antipsychotics aripiprazole and lurasidone, the anxiolytic buspirone, and several novel agents such as cariprazine and brexpiprazole.[7,8,10]

5HT1B and 5HT1D

Serotonin 5HT1B receptors exist both as postsynaptic autoreceptors on the axons of nonserotonergic cells and as presynaptic autoreceptors on the axons of serotonergic neurons. Serotonin 5HT1B heteroreceptors control release of ACh from neurons in the basal forebrain, HA from neurons in the tuberomamillary nucleus, DA from neurons in the ventral tegmental area, and NE from neurons in the locus coeruleus.[4,11] Blockade of 5HT1B postsynaptic heteroreceptors may also have antidepressant effects due to resultant increases in Glu, DA, ACh, NE, and HA in the cortex.[4,8] Serotonin 5HT1B autoreceptors function much the same as 5HT1A autoreceptors (discussed in the previous section); stimulation of 5HT1B autoreceptors reduces 5HT output.[7,11] Serotonin 5HT1D receptors also function as autoreceptors on serotonergic axons and have historically been difficult to distinguish from 5HT1B receptors due to a lack of selective agonists and antagonists, species differences, and confusion in nomenclature.[12] Although 5HT1B receptors may be more prominent in median raphe nuclei, whereas 5HT1D receptors are more abundant in dorsal raphe nuclei, they are often lumped together as 5HT1B/1D when discussing the function of serotonergic autoreceptors (Figure 3).[13]

5HT2A

Serotonin 5HT2A receptors are located throughout the brain, including the cerebral, piriform, and entorhinal cortices; claustrum; olfactory bulb; anterior olfactory nucleus; brainstem nuclei; and limbic regions.[6] Within the cortex, 5HT2A receptors are located on Glu and GABA neurons.[7] Serotonin 5HT2A receptors may be increased in patients with MDD, and it has been shown that chronic treatment with 5HT2A antagonists results in down-regulation of the 5HT2A receptor in conjunction with antidepressant effects.[8] The antidepressant effects, as well as amelioration of antipsychotic-induced EPS, from 5HT2A antagonism are thought to stem, at least partially, from disinhibition of dopaminergic neurons and the resultant increase in cortical DA neurotransmission (Figure 4).[4,6]

5HT2C

Serotonin 5HT2C receptors are found in numerous brain regions including the hippocampus, amygdala, anterior

https://doi.org/10.1017/S1092852914000613 Published online by Cambridge University Press

TABLE 1. Serotonin receptors

		Mechanism of therapeutic actions			Psychotropic agents with binding affinity	
Serotonin receptor	Molecular actions	Agonism/partial agonism	Antagonism	Theoretical symptom targets and clinical relevance	Available	In development
5HT1A	Gi/o-coupled	X		Depression; drug-induced EPS; acceleration of antidepressant effects	Aripiprazole Clozapine Lurasidone Quetiapine Vilazodone Vortioxetine	Cariprazine Brexpiprazole Adoprazine SSR181507 F15063 F15599
5HT1B	Gi/o-coupled		X	Acceleration of antidepressant effects	Aripiprazole Asenapine Clozapine Iloperidone Quetiapine Ziprasidone Vortioxetine	GR127935 SB 216641
5HT2A	Gq-coupled		X	Depression; drug-induced EPS	Aripiprazole Asenapine Clozapine Iloperidone Lurasidone Olanzapine Paliperidone Risperidone Quetiapine Ziprasidone Mirtazapine Trazodone Pimavanserin	
5HT2C	Gq-coupled	X	X	Depression	Asenapine Clozapine Olanzapine Quetiapine Agomelatine Fluoxetine Mirtazapine Mianserin Nefazodone Trazodone Lorcaserin	
5HT3	Ion channel		X	Cognitive impairment; anxiety; drug-induced gastrointestinal issues	Clozapine Fluoxetine Mirtazapine Vortioxetine	Tropisetron Ondansetron Granisetron
5HT4	Gs-coupled	X		Cognitive impairment		Tropisetron RS67333 PRX-3140 PF-04995274 RQ-9
5HT6	Gs-coupled	X	X	Depression; cognitive impairment	Asenapine Clozapine Olanzapine Quetiapine Clomipramine Amitriptyline Doxepin Mianserin	Antagonists SB-399885 SB-742457 Lu-AE-58054 P7C3 SUVN-502 Agonists LY-586713 WAY-181187 WAY-208466
5HT7	Gs-coupled		X	Depression; cognitive impairment; circadian dysregulation	Aripiprazole Asenapine Clozapine Lurasidone Paliperidone Risperidone Quetiapine Ziprasidone Amisulpride Amoxapine Desipramine Imipramine Mianserin Fluoxetine Vortioxetine	

https://doi.org/10.1017/S1092852914000613 Published online by Cambridge University Press

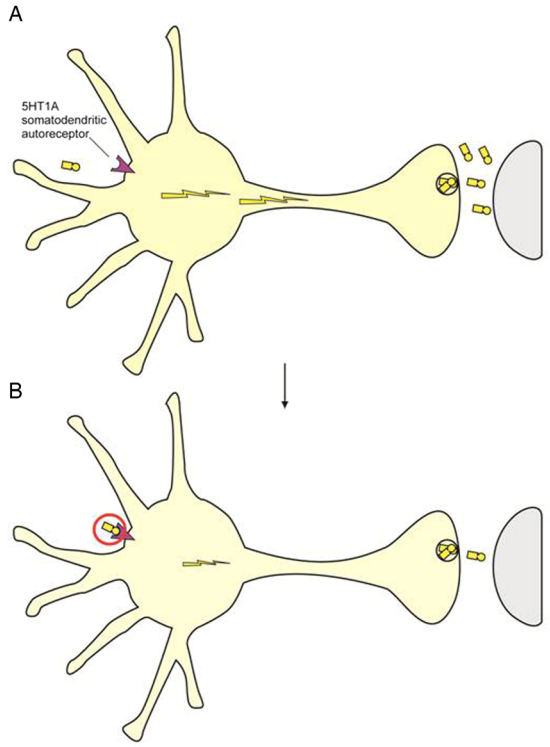

FIGURE 2. Serotonin 5HT1A somatodendritic autoreceptors. (A) Presynaptic 5HT1A autoreceptors are located on the soma and dendrites of serotonergic neurons. (B) Serotonin (5HT) binding to 5HT1A autoreceptors causes inhibition of neuronal impulses and a reduction in 5HT output.

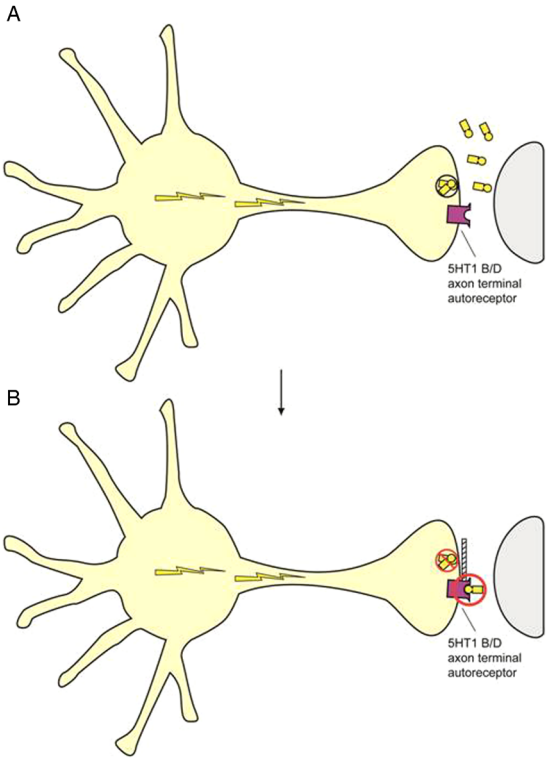

FIGURE 3. Serotonin 5HT1B/D axon terminal autoreceptors. (A) Presynaptic 5HT1B/D autoreceptors are located on presynaptic axon terminals of serotonergic neurons. (B) Binding of 5HT to 5HT1B/D autoreceptors causes inhibition of 5HT release.

olfactory and endopiriform nuclei, cingulate and piriform cortices, thalamic nuclei, and substantia nigra.[6–9] Although preferentially located on GABAergic interneurons, 5HT2C receptors can also be found on DA neurons in the mesolimbic pathway.[7] Interestingly, both 5HT2C agonists and antagonists have been shown to have antidepressant effects.[8] This seemingly conflicting information may be due to the fact that antagonists block the actions of 5HT2C receptors, whereas chronic agonism of 5HT2C receptors leads to receptor downregulation; in both scenarios, there may a resultant increase in DA and NE in terminal regions.[4]

5HT3

Serotonin 5HT3 receptors are found in the spinal cord, brainstem, hippocampus, and amygdala, and the entorhinal, frontal, and cingulate cortices where they regulate DA, NE, 5HT, ACh, GABA, and HA release (Figure 5).[7,8] Serotonin 5HT3 receptors also modulate pyramidal cell activity in the cortex by reducing Glu neurotransmission (Figure 6).[4] Data have shown that antagonism of the 5HT3 receptor may have several therapeutic effects, including enhanced cognition and reduced anxiety, as well as reducing D2-antagonism–induced EPS.[6–9] Additionally, antagonism of 5HT3 receptors in the chemoreceptor trigger zone of the brainstem and in the gastrointestinal tract, which mediate nausea/vomiting and bowel motility, may protect against the gastrointestinal side effects that often accompany antidepressant agents such as SSRIs and SNRIs.[4,6]

5HT4

Serotonin 5HT4 receptors, which are located in the putamen, caudate nucleus, hippocampus, nucleus accumbens, globus pallidus, substantia nigra, neocortex, raphe and pontine nuclei, and thalamus, are thought to mediate the expression of various genes involved in synaptic plasticity.[6–8] In line with this hypothesis, 5HT4 agonists have been shown to enhance cognition, whereas 5HT4 antagonists may cause impairments in learning and memory.[6] Not only does stimulation of 5HT4 receptors increase release of ACh, it also may reduce the levels of amyloid beta.[10] Amyloid beta is the protein that accumulates in Alzheimer's disease, a neurodegenerative condition that is often heralded by depression in its earlier stages.[14]

5HT6

Serotonin 5HT6 receptors are located in the striatum, nucleus accumbens, olfactory tubercles, cortex, hippocampus, amygdala, hypothalamus, thalamus, and cerebellum,

https://doi.org/10.1017/S1092852914000613 Published online by Cambridge University Press

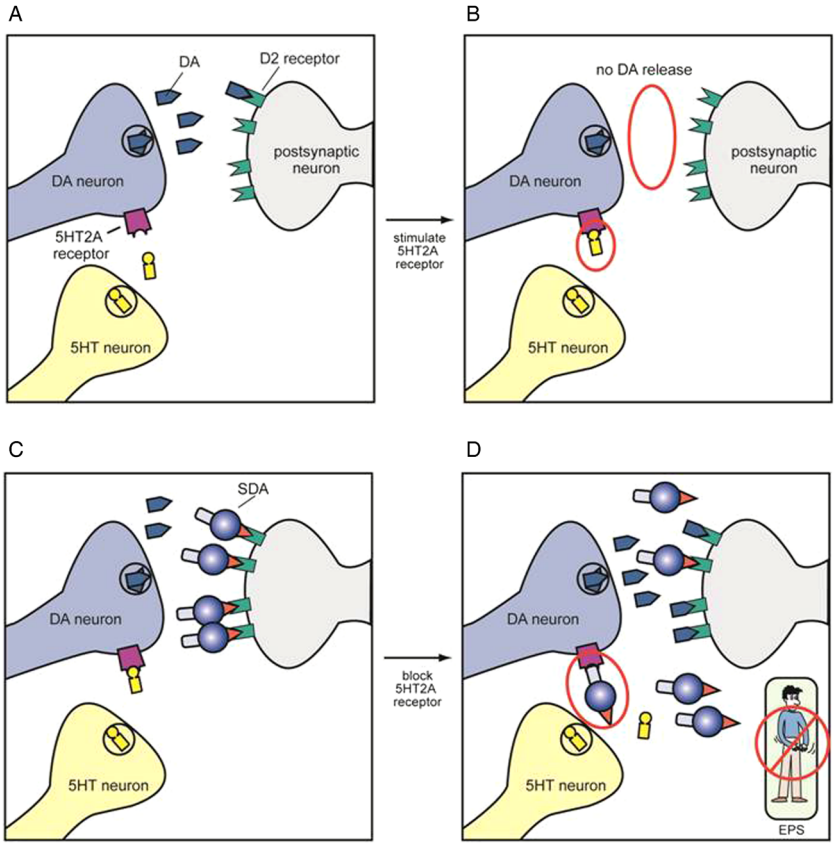

FIGURE 4. Serotonin 5HT2A receptors in the nigrostriatal pathway. (A, B) Binding of 5HT to 5HT2A receptors located on nigrostriatal dopaminergic neurons leads to inhibition of DA neurotransmission. (C) Atypical antipsychotics, which are essentially serotonin-dopamine antagonists (SDAs), block the actions of dopamine at postsynaptic DA receptors; this can lead to the development of extrapyramidal symptoms (EPS). (D) However, simultaneous blockade of 5HT2A receptors leads to an increase in DA output. This excessive DA in the nigrostriatal pathway is able to compete with binding of atypical antipsychotics to DA receptors, thus ameliorating EPS.

where they regulate the release of ACh, NE, DA, and GABA.[7–10] These receptors have been implicated in many psychiatric illnesses, including schizophrenia, eating disorders, cognitive impairment, and depression.[4,6] Interestingly, both agonism and antagonism of 5HT6 receptors may have both pro-cognitive and antidepressant effects.[7,8,10]

5HT7

Serotonin 5HT7 receptors, located in the thalamus, hypothalamus, hippocampus, and cortex, have been implicated in thermoregulation, circadian rhythms, sleep, and mood disorders.[4,6,8] Intriguingly, dysregulation of circadian rhythms and sleep-wake disorders are highly prevalent in patients with MDD.[15,16] Therefore, the antidepressant effects of 5HT7 antagonism may be due not only to increases in 5HT levels and activation of glutamatergic neurons in the PFC, but also to normalization of circadian rhythms (Figure 7).[17] Additionally, the 5HT7 receptor has been implicated as an important mediator of hippocampus-dependent learning and memory; thus modulation of the 5HT7 receptor may also affect the impaired cognition that is often present in patients with MDD.[18]

Reuptake Inhibitors

The most commonly prescribed antidepressant treatments, SSRIs and SNRIs, work by blocking the reuptake of 5HT and NE from the synapse, leaving more of these neurotransmitters available to bind to their respective receptors and mediate downstream effects on mood, cognition, anxiety, and many other functions (Figure 8).[4] However, although reuptake inhibitors rapidly increase monoamine levels upon treatment initiation, the therapeutic effects can take weeks to manifest.[4,19] The reason for this may be due to the inhibitory effects of 5HT autoreceptor stimulation.[4,5] The initial increase in a monoamine (eg, 5HT) following treatment with an antidepressant (eg, an SSRI) results in activation of 5HT1A, 5HT1B, and 5HT1D autoreceptors, which in turn causes a decrease in 5HT output (Figure 9).[4,7,9] With time, 5HT1A, 5HT1B, and 5HT1D receptors may be down-regulated and/or desensitized, leading to

https://doi.org/10.1017/S1092852914000613 Published online by Cambridge University Press

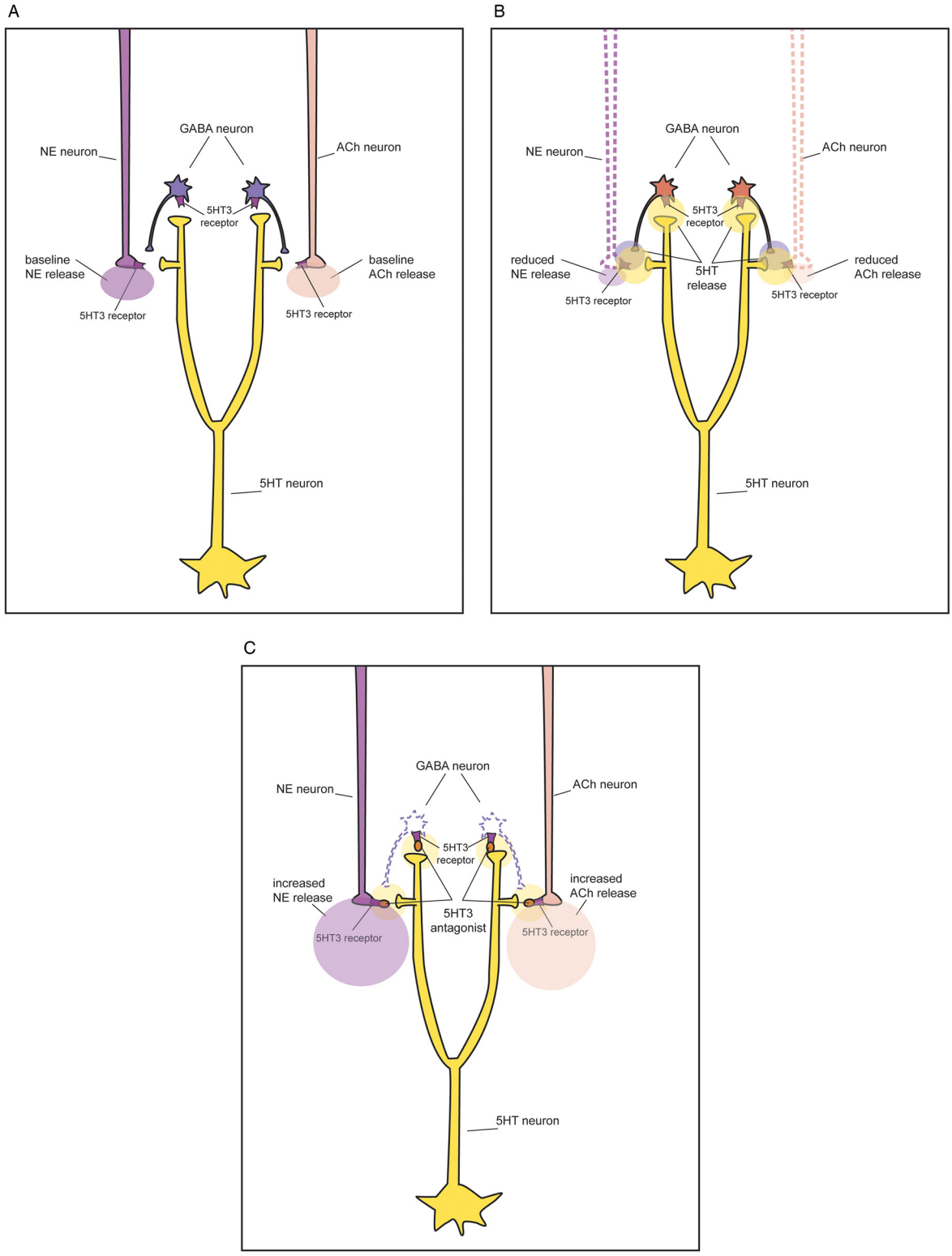

FIGURE 5. Effects of serotonin 5HT3 receptors on ACh and NE neurotransmission. (A, B) When 5HT binds to 5HT3 receptors on GABAergic neurons, GABA is released onto cholinergic and noradrenergic neurons preventing the release of acetylcholine (ACh) and norepinephrine (NE), respectively. Additionally, the binding of 5HT to postsynaptic 5HT3 receptors located on directly on cholinergic and noradrenergic neurons also prevents release of ACh and NE. (C) Administration of a 5HT3 antagonist leads to disinhibition of cholinergic and noradrenergic neurons, thus increased ACh and NE output.

https://doi.org/10.1017/S1092852914000613 Published online by Cambridge University Press

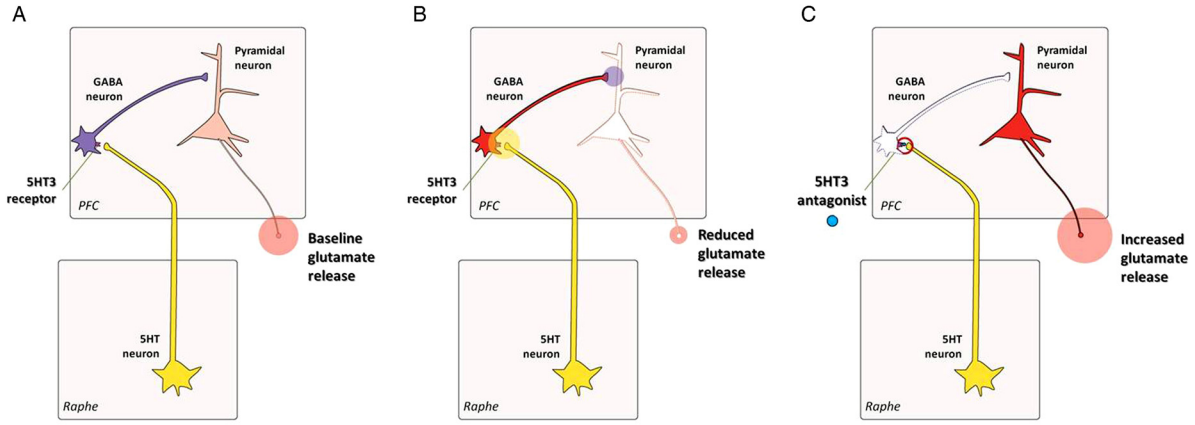

FIGURE 6. Effects of serotonin 5HT3 receptors on Glu neurotransmission. (A) Serotonin 5HT3 receptors are found on GABAergic neurons in the prefrontal cortex (PFC). (B) When 5HT binds to these 5HT3 receptors, GABAergic neurons are stimulated and release GABA onto glutamatergic neurons, thus inhibiting Glu output. (C) Addition of a 5HT3 antagonist inhibits GABA from being released, thus increasing Glu neurotransmission.

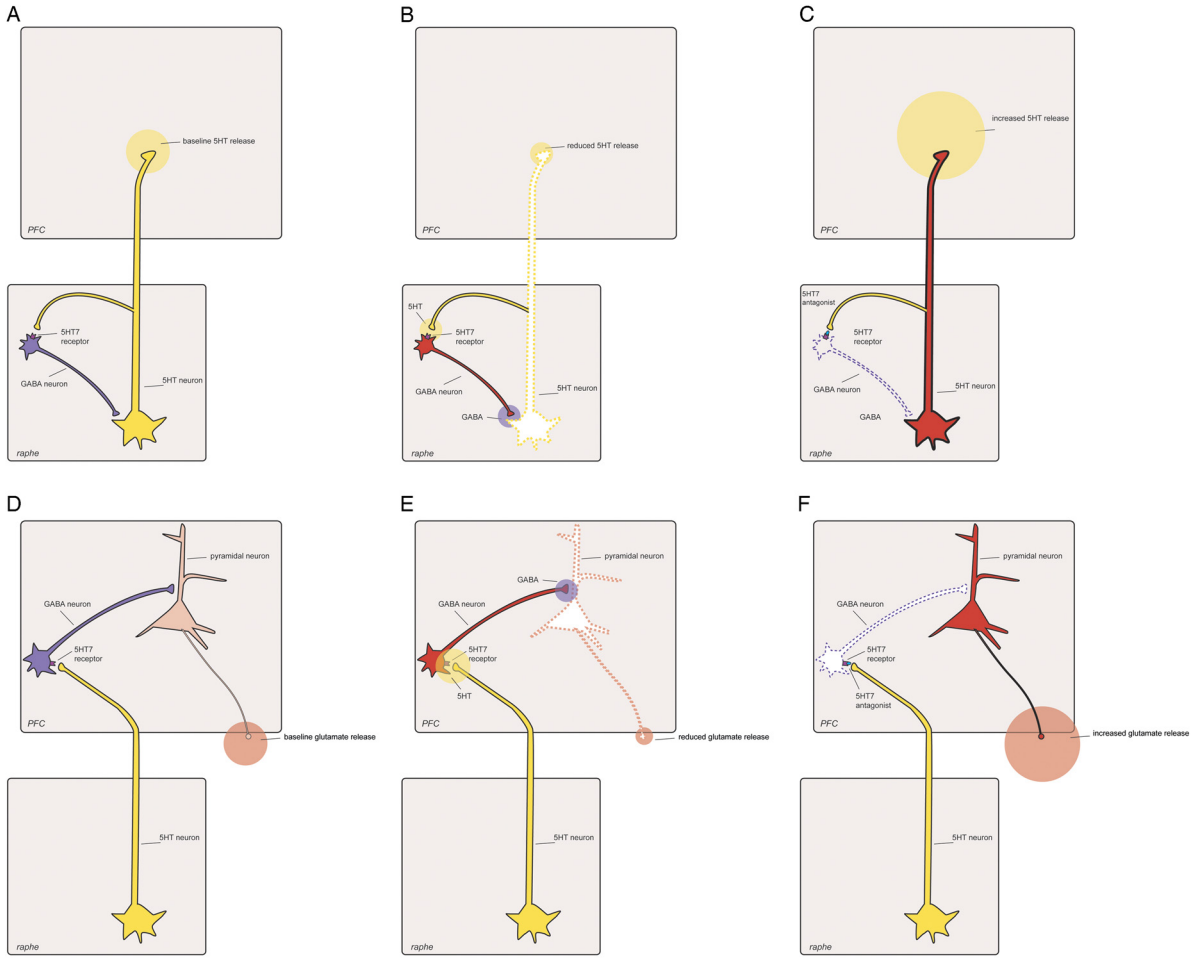

FIGURE 7. Serotonin 5HT7 receptors. (A) Serotonin 5HT7 receptors are located on GABAergic neurons in the raphe nuclei. (B) When stimulated by 5HT, these 5HT7 receptors activate GABAeric neurons, leading to inhibition of 5HT output in the prefrontal cortex (PFC). (C) Addition of a 5HT7 antagonist blocks activation of GABAergic neurons in the raphe nuclei, leading to disinhibition of serotonergic neurons and increased 5HT output. (D) Similarly, 5HT7 receptors are also located on GABAergic neurons in the PFC where they regulate activation of glutamatergic neurons. (E) When these 5HT7 receptors are activated by 5HT, GABA is released onto glutamatergic neurons, inhibiting release of Glu. (E) When a 5HT7 antagonist is added, GABAergic neurons are not activated, glutamatergic neurons are disinhibited, and Glu output is increased.

https://doi.org/10.1017/S1092852914000613 Published online by Cambridge University Press

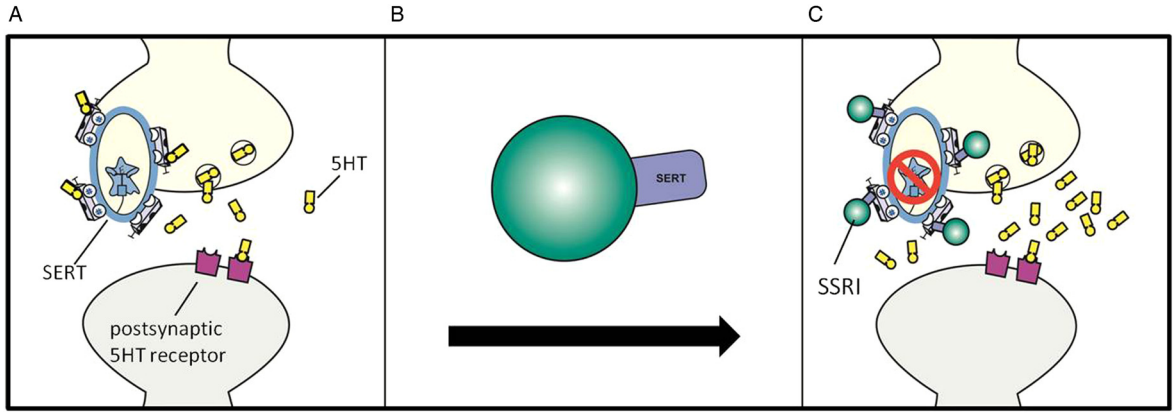

FIGURE 8. Serotonin reuptake transporter inhibition. (A) The serotonin reuptake transporter (SERT) removes 5HT from the synapse leaving less 5HT to act on serotonergic receptors. (B) Many antidepressants and some atypical antipsychotics have binding affinity for SERT. (C) Administration of a pharmacological agent with SERT binding affinity, such as a selective serotonin reuptake inhibitor (SSRI), prevents SERT from pumping 5HT out of the synapse, leaving more 5HT available to bind 5HT receptors and exert downstream effects on neurotransmission and behavior.

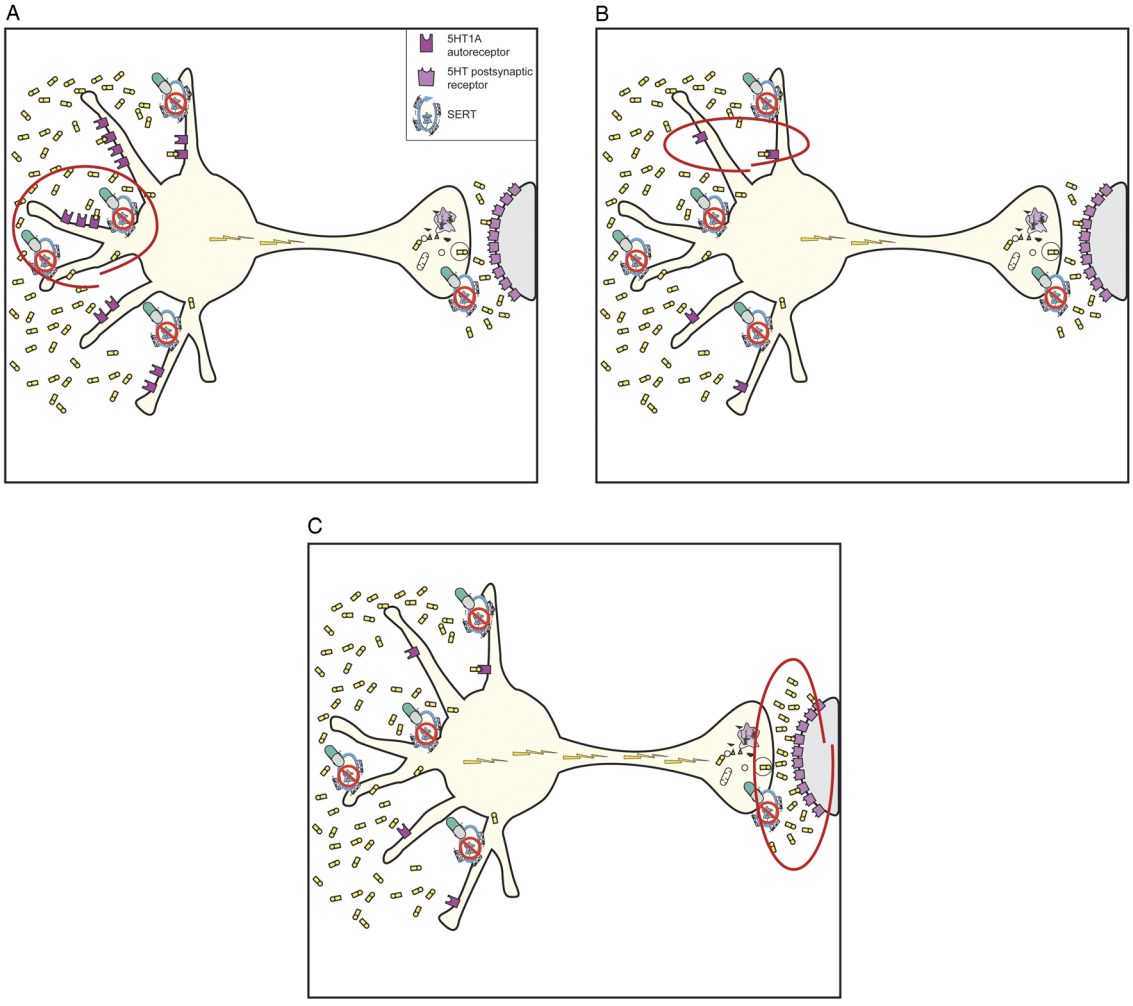

FIGURE 9. Delayed therapeutic actions of SERT inhibitors. (A) In the depressed state, 5HT levels are hypothetically low, 5HT receptors are upregulated, and stimulation of the serotonergic neuron to increase 5HT output are low. Upon administration of a SERT inhibitor (eg, an SSRI), reuptake of 5HT is prevented at both the dendrites (left) and at the axon (right). (B) Although 5HT levels may be immediately increased, 5HT binds to somatodendritic 5HT1A autoreceptors (as well as 5HT1B/D axonal autoreceptors—not shown), inhibiting further release of 5HT. (C) Eventually, 5HT1A (and 5HT1B/D) autoreceptors are downregulated and/or desensitized leading to increased 5HT output. This necessity for downregulation/desensitization of autoreceptors is thought to underlie the delay in therapeutic actions of SSRIs.

https://doi.org/10.1017/S1092852914000613 Published online by Cambridge University Press

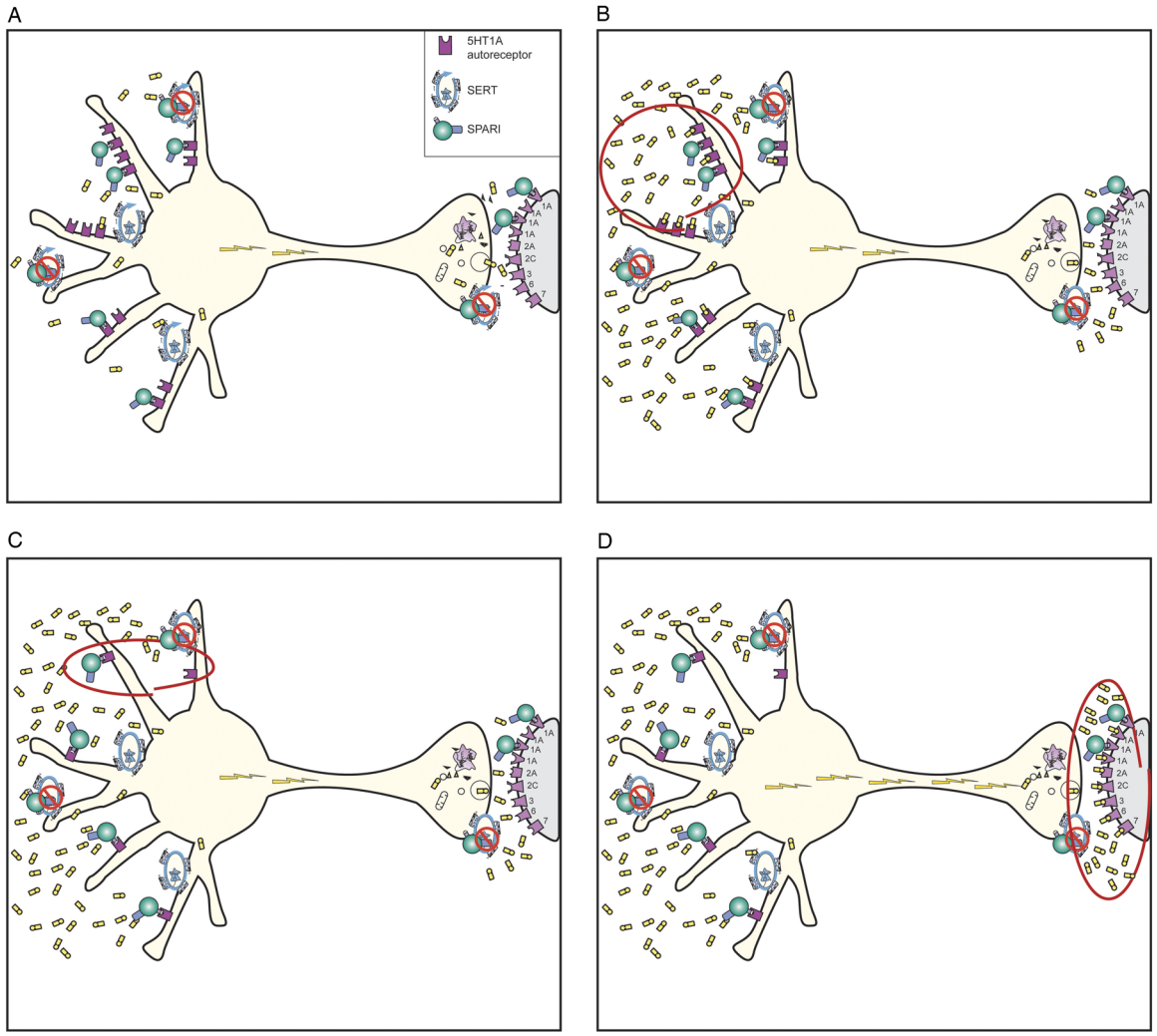

FIGURE 10. Simultaneous inhibition of SERT and 5HT autoreceptors may reduce therapeutic delay of antidepressant treatment. (A) Some novel multimodal agents, such as serotonin partial agonist/reuptake inhibitors (SPARIs), combine SERT inhibition with antagonism or partial agonism of 5HT autoreceptors. (B) The inhibitory actions at SERT cause an increase in somatodendritic 5HT levels, which would bind 5HT1A autoreceptors. (C) Downregulation of 5HT1A autoreceptor levels from the increased somatodendritic 5HT would normally be delayed if SERT inhibition was the sole pharmacological intervention. However, the presence of a 5HT1A partial agonist blocks 5HT from binding to 5HT1A autoreceptors and theoretically leads to more a more rapid downregulation and/or desensitization of 5HT1A autoreceptors. (D) The dual actions at SERT and 5HT autoreceptors therefore lead to a more rapid increase in axonal 5HT output and subsequent therapeutic effects.

increased 5HT output, stimulation of postsynaptic 5HT receptors, and therapeutic effects.[4] One strategy with the potential for decreasing the delay between SERT inhibition and therapeutic effects is to simultaneously block 5HT1A, 5HT1B, and/or 5HT1D autoreceptors; this can be achieved either by combining multiple pharmacological agents or by using a single agent with actions at both reuptake pumps and multiple 5HT receptors.

Polypharmacy and Multimodal Agents

As discussed above, the most commonly employed treatments for MDD (SSRIs and SNRIs) often take weeks to reach full therapeutic effectiveness, leaving patients suffering with unresolved symptoms of depression in the meantime. Simultaneous blockade of 5HT autoreceptors and SERT may accelerate the therapeutic benefit of antidepressant treatment by preventing the inhibition of 5HT neurons that follows the initial burst of serotonin (Figure 10).[4,7,8] Indeed, this is the rationale for adding an agent such as pindolol, a partial agonist at 5HT1A and 5HT1B receptors, as an adjunct to antidepressant treatment.[8] Binding affinity for 5HT1A and 5HT1B/D is also a property of many atypical antipsychotics and, along with binding at various other 5HT receptors, may contribute to the efficacy of some of these agents in treating depression (Table 2).[4] The newly approved antidepressants vilazodone and vortioxetine, as well as several other agents in development, are multimodal

https://doi.org/10.1017/S1092852914000613 Published online by Cambridge University Press

TABLE 2. Potential antidepressant mechanisms of atypical antipsychotics*

	SERT	NET	DAT	5HT1A	5HT1B/D	5HT2A	5HT2C	5HT3	5HT7	Alpha2
Aripiprazole										
Asenapine										
Brexpiprazole										
Cariprazine										
Clozapine										
Iloperidone										
Lurasidone										
Olanzapine										
Paliperidone										
Quetiapine/ Norquetiapine										
Risperidone										
Ziprasidone										

5HT: serotonin; DAT: dopamine reuptake transporter; NET: norepinephrine reuptake transporter; SERT: serotonin reuptake transporter.

TABLE 3. Potential antidepressant mechanisms of novel agents*

	SERT	NET	DAT	5HT1A	5HT1B/D	5HT2C	5HT3	5HT7	MT
Agomelatine									
Amitifadine									
Buspirone									
Edivoxetine									
Lisdexamfetamine									
Vilazodone									
Vortioxetine									

5HT: serotonin; DAT: dopamine reuptake transporter; MT: melatonergic; NET: norepinephrine reuptake transporter; SERT: serotonin reuptake transporter.

agents that also take advantage of the potential for simultaneously inhibiting SERT while stimulating or blocking specific 5HT receptors (Table 3).[19] Although the theory that novel multimodal agents acting on various 5HT receptors and SERT may accelerate the antidepressant effects compared to traditional treatments (eg, SSRIs) has been supported in animal models, it remains to be seen whether this theory will play out in clinical situations.

Conclusion

Inhibition of reuptake transporters, especially of SERT, has been the mainstay of antidepressant treatment for several decades. The antidepressant actions of SSRIs and SNRIs are thought to stem from their ability to compensate for an underlying monoamine deficiency inherent to MDD. However, as our knowledge of the serotonergic system has increased, we are beginning to fully recognize that it is not enough simply to raise 5HT levels; we must also consider the various 5HT receptor targets and their downstream actions when designing optimal therapeutics. By simultaneous blocking or stimulating specific 5HT receptors, we can fine-tune pharmacologic treatment and potentially provide more effective and faster treatments with reduced propensity for intolerable side effects (Table 1). For example, if a patient with MDD is experiencing impairments in memory, a rationale strategy might include choosing a pharmacological agent with strong affinity for 1 or more 5HT receptors implicated in cognition, such as 5HT3, 5HT4, 5HT6, and 5HT7.

* Please note that the labeling of Tables 2 and 3 has been corrected since the original publication of this article. An erratum notice detailing this change was also published (DOI 10.1017/S1092852915000097).

https://doi.org/10.1017/S1092852914000613 Published online by Cambridge University Press

As our understanding of the 5HT system continues to expand and our repertoire of pharmacological agents with targeted binding affinity for specific 5HT receptors is increased, it is likely that the future will bring more effective, more tolerable, and faster-acting treatments for patients suffering with depression.

Disclosures

Debbi Morrisette does not have anything to disclose. Stephen M. Stahl, MD, PhD: Over the past 12 months (March 2013–April 2014), Dr. Stahl has served as a consultant for Astra Zeneca, Avanir, Biomarin, Envivo, Forest, Jazz, Lundbeck, Neuronetics, Noveida, Orexigen, Otsuka, PamLabs, Servier, Shire, Sunovion, Taisho, Takeda and Trius; he is a board member of RCT Logic and GenoMind; he is on the speakers bureau for Astra Zeneca, Janssen, Otsuka, Sunovion, and Takeda; and he has received research and/or grant support from AssureX, Eli Lilly, EnVivo, Janssen, JayMac, Jazz, Lundbeck, Mylan, Neuronetics, Novartis, Otsuka, Pamlabs, Pfizer, Roche, Shire, Sunovion, Takeda, Teva, and Valeant.

REFERENCES:

1. US Burden of Disease Collaborators. The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. *JAMA*. 2013; **310**(6): 591–608.
2. Bulloch A, Williams J, Lavorato D, Patten S. Recurrence of major depressive episodes is strongly dependent on the number of previous episodes. *Depress Anxiety*. 2014; **31**(1): 72–76.
3. Marazziti D. Depression and serotonin: a never ending story. *Curr Drug Targets*. 2013; **14**(5): 513.
4. Stahl SM. *Stahl's Essential Psychopharmacology*. 4th ed. New York: Cambridge University Press; 2013.
5. Mann JJ. The serotonergic system in mood disorders and suicidal behaviour. *Philos Trans R Soc Lond B Biol Sci*. 2013; **368**(1615): 20120537.
6. Shimizu S, Mizuguchi Y, Ohno Y. Improving the treatment of schizophrenia: role of 5-HT receptors in modulating cognitive and extrapyramidal motor functions. *CNS Neurol Disord Drug Targets*. 2013; **12**(6): 861–869.
7. Artigas F. Serotonin receptors involved in antidepressant effects. *Pharmacol Ther*. 2013; **137**(1): 119–131.
8. Carr GV, Lucki I. The role of serotonin receptor subtypes in treating depression: a review of animal studies. *Psychopharmacology (Berl)*. 2011; **213**(2–3): 265–287.
9. Ohno Y, Shimizu S, Tokudome K. Pathophysiological roles of serotonergic system in regulating extrapyramidal motor functions. *Biol Pharm Bull*. 2013; **36**(9): 1396–1400.
10. Ramirez MJ, Lai MK, Tordera RM, Francis PT. Serotonergic therapies for cognitive symptoms in Alzheimer's disease: rationale and current status. *Drugs*. 2014; **74**(7): 729–736.
11. Sari Y. Serotonin1B receptors: from protein to physiological function and behavior. *Neurosci Biobehav Rev*. 2004; **28**(6): 565–582.
12. Bonaventure P, Kelly L, Aluisio L, *et al*. Selective blockade of 5-hydroxytryptamine (5-HT)7 receptors enhances 5-HT transmission, antidepressant-like behavior, and rapid eye movement sleep suppression induced by citalopram in rodents. *J Pharmacol Exp Ther*. 2007; **321**(2): 690–698.
13. Hopwood SE, Stamford JA. Multiple 5-HT(1) autoreceptor subtypes govern serotonin release in dorsal and median raphe nuclei. *Neuropharmacology*. 2001; **40**(4): 508–519.
14. Khundakar AA, Thomas AJ. Neuropathology of depression in Alzheimer's disease: current knowledge and the potential for new treatments. *J Alzheimers Dis*. Epub ahead of print.
15. Baron KG, Reid KJ. Circadian misalignment and health. *Int Rev Psychiatry*. 2014; **26**(2): 139–154.
16. Karatsoreos IN. Links between circadian rhythms and psychiatric disease. *Front Behav Neurosci*. 2014; **8**: 162.
17. Tokarski K, Kusek M, Sowa J, Bobula B. Possible involvement of 5-HT7 receptor in pathophysiology of affective disorders and action of antidepressant drugs. *Postepy Hig Med Dosw (Online)*. 2014; **68**: 1104–1113.
18. Roberts AJ, Hedlund PB. The 5-HT(7) receptor in learning and memory. *Hippocampus*. 2012; **22**(4): 762–771.
19. Stahl SM, Lee-Zimmerman C, Cartwright S, Morrissette DA. Serotonergic drugs for depression and beyond. *Curr Drug Targets*. 2013; **14**(5): 578–585.

https://doi.org/10.1017/S1092852914000613 Published online by Cambridge University Press

CME Posttest and Certificate

CME Credit Expires: November 30, 2017

CME Posttest Study Guide

NOTE: The posttest can only be submitted online. *The below posttest questions have been provided solely as a study tool to prepare for your online submission.* ***Faxed/mailed copies of the posttest cannot be processed*** *and will be returned to the sender. If you do not have access to a computer, contact NEI customer service at 888-535-5600.*

1. A 24-year-old man with major depressive disorder has been taking the selective serotonin reuptake inhibitor, fluoxetine, for 10 days with no therapeutic benefit. One novel strategy for potentially reducing the delay in therapeutic effect from serotonin reuptake inhibition is to add an agent with 5HT1B/D antagonism. Serotonin 5HT1B/D autoreceptors are located on:

   A. Axons of serotonergic neurons
   B. Soma and dendrites of serotonergic neurons
   C. Both A and B
   D. Neither A nor B

2. A 51-year-old female patient with treatment-resistant depression was recently initiated on the atypical antipsychotic quetiapine as an adjunct to her antidepressant treatment. Quetiapine may have antidepressant qualities due to its binding affinity for:

   A. Serotonin reuptake transporters (SERT)
   B. Serotonin 5HT3 receptors
   C. Serotonin 5HT7 receptors

3. Jackson is a 32-year-old patient with major depressive disorder who was recently initiated on the multimodal antidepressant vortioxetine. The antidepressant effects of vortioxetine are thought to be due to its binding affinity for:

   A. Serotonin reuptake transporters (SERT)
   B. Serotonin 5HT1A receptors
   C. Serotonin 5HT3 receptors
   D. All of the above
   E. None of the above

CME Online Posttest and Certificate

To receive your certificate of CME credit or participation, complete the posttest and activity evaluation, available only online at **www.neiglobal.com/CME** under ''CNS Spectrums''. If a score of 70% or more is achieved, you will be able to immediately print your certificate. There is no posttest fee nor fee for CME credits for this activity. Questions? call 888-535-5600, or email customerservice@neiglobal.com.

https://doi.org/10.1017/S1092852914000613 Published online by Cambridge University Press