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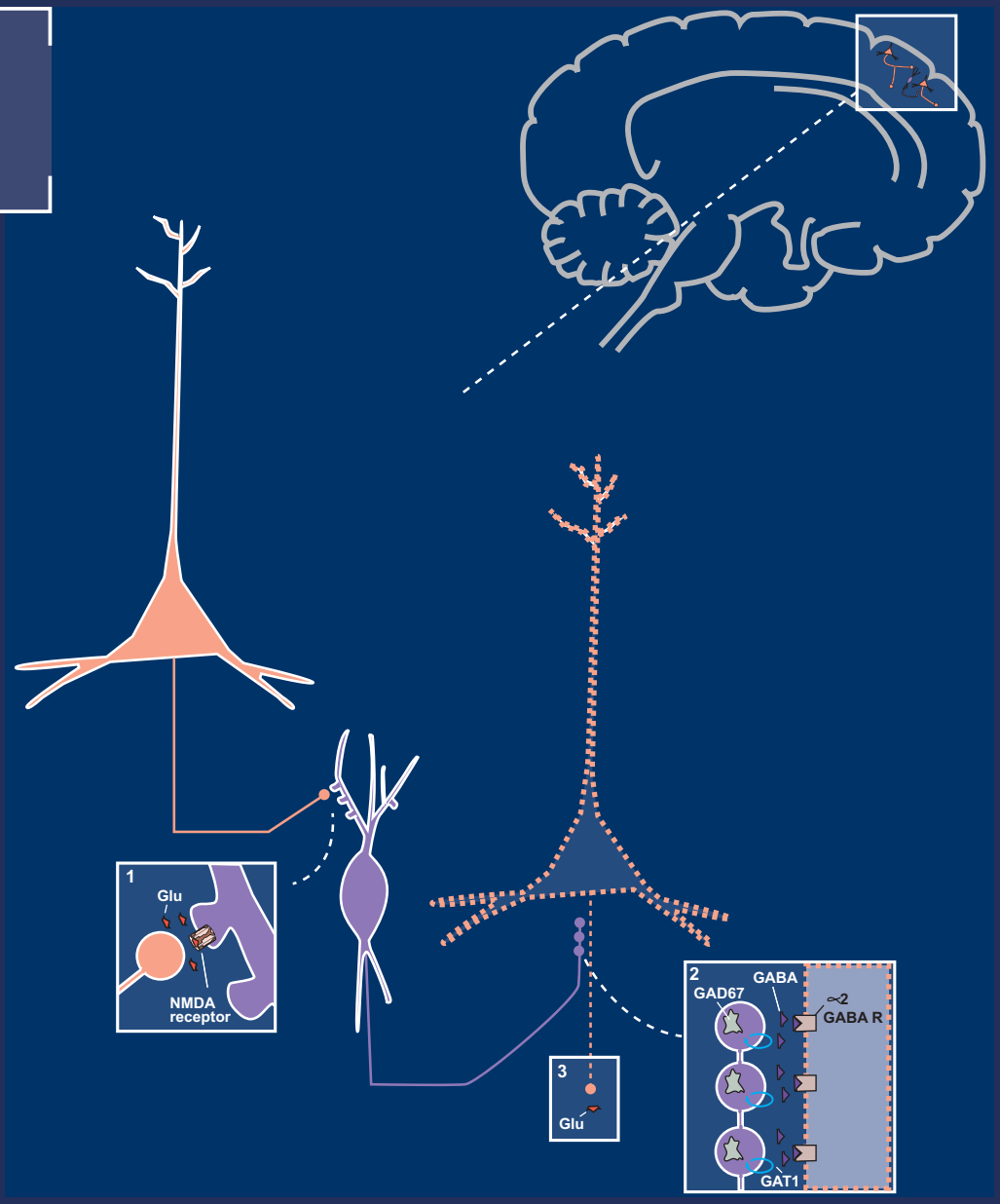

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CNS SPECTRUMS

EDITOR-IN-CHIEF: **STEPHEN M. STAHL**

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NUEDEXTA®
(dextromethorphan HBr and quinidine sulfate) capsules 20 mg / 10 mg

APPROVED SINCE
2010[1]
Over 1,000,000 prescriptions[a]

[a]IMS Health data, 2015.[2]

IN PATIENTS WITH NEUROLOGIC CONDITIONS OR BRAIN INJURY

LOOK BELOW THE SURFACE: HE MAY HAVE PBA

- An estimated 7 million people with neurologic conditions (eg, dementia, stroke, traumatic brain injury) have symptoms suggestive of pseudobulbar affect (PBA)[b,c,3]
- NUEDEXTA is the first—and only—FDA-approved treatment for PBA[1]

PBA is often mischaracterized as depression[4-6]

START SCREENING FOR PBA WITH THE *SINGLE SCREENING QUESTION*[d,7]:

Have you ever experienced involuntary episodes of crying and/or laughing that were exaggerated or even contrary to how you felt at the time?

[d]A clinical diagnosis is required to determine if a patient has PBA.

Visit NUEDEXTA.com or call 1-855-4NUEDEX (468-3339).

Indications and Usage

NUEDEXTA is indicated for the treatment of pseudobulbar affect (PBA).

PBA occurs secondary to a variety of otherwise unrelated neurologic conditions, and is characterized by involuntary, sudden, and frequent episodes of laughing and/or crying. PBA episodes typically occur out of proportion or incongruent to the underlying emotional state. PBA is a specific condition, distinct from other types of emotional lability that may occur in patients with neurological disease or injury.[1]

Important Safety Information

NUEDEXTA (dextromethorphan hydrobromide and quinidine sulfate) 20mg/10mg capsules can interact with other medications causing significant changes in blood levels of those medications and/or NUEDEXTA which may lead to serious side effects. Adjust dose or use alternate treatment of the other medication when clinically indicated.

NUEDEXTA is contraindicated in patients concomitantly taking: QT-prolonging drugs metabolized by CYP2D6 (e.g., thioridazine and pimozide); monoamine oxidase inhibitors (MAOIs) within the preceding or following 14 days; other drugs containing quinidine, quinine, or mefloquine and in patients with a known hypersensitivity to these drugs or any of NUEDEXTA's components.

Discontinue use of NUEDEXTA if hepatitis, thrombocytopenia, serotonin syndrome or a hypersensitivity reaction occurs.

NUEDEXTA is contraindicated in patients with certain risk factors for arrhythmia: Prolonged QT interval; congenital long QT syndrome, history suggestive of torsades de pointes; heart failure; complete atrioventricular (AV) block or risk of AV block without an implanted pacemaker.

NUEDEXTA causes dose-dependent QTc prolongation. When initiating NUEDEXTA in patients at risk for QT prolongation and torsades de pointes, electrocardiographic (ECG) evaluation should be conducted at baseline and 3-4 hours after the first dose. Risk factors include left ventricular hypertrophy or dystrophy or concomitant use of drugs that prolong QT interval or certain CYP3A4 inhibitors.

The most common adverse reactions are diarrhea, dizziness, cough, vomiting, asthenia, peripheral edema, urinary tract infection, influenza, increased gamma-glutamyltransferase, and flatulence. NUEDEXTA may cause dizziness. Precautions to reduce the risk of falls should be taken, particularly for patients with motor impairment affecting gait or a history of falls.

These are not all the risks from use of NUEDEXTA.

Please refer to the adjacent page for the brief summary of the Full Prescribing Information or useful prescribing information at www.NUEDEXTA.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088.

[b]When considering patients with any of the 6 common neurologic conditions associated with PBA, it is estimated that PBA symptoms occur in 37% of patients, or an estimated 7.1 million Americans, with CNS-LS scores ≥13 and in 9.3% of patients, or an estimated 1.8 million Americans, with CNS-LS scores ≥21.[8]

[c]In the PRISM study, the presence of PBA symptoms was defined as a CNS-LS score ≥13 and merits further diagnostic assessment. A more restrictive definition was also evaluated using a CNS-LS ≥21. The CNS-LS was validated as a PBA screening tool in ALS and MS populations.[9-11]

References: 1. NUEDEXTA Prescribing Information, Avanir Pharmaceuticals, Inc. **2.** Data on file. Avanir Pharmaceuticals, Inc. **3.** Work SS, et al. *Adv Ther*. 2011;28:586-601. **4.** Crumpacker DW, et al. *US Neurol*. 2014;10:10-14. **5.** Ahmed A, et al. *Ther Clin Risk Manag*. 2013;9:483-489. **6.** Colamonico J, et al. *Adv Ther*. 2012;29:775-798. **7.** Fonda JR, et al. *J Rehabil Res Dev*. 2015;52:839-850. **8.** Brooks BR, et al. *PLoS One.* 2013;8:e72232. **9.** Moore SR, et al. *J Neurol Neurosurg Psychiatry.* 1997;63:89-93. **10.** Smith RA, et al. *Amyotroph Lateral Scler Other Motor Neuron Disord.* 2004;5(suppl 1):99-102. **11.** Smith RA, et al. *Mult Scler.* 2004;10:679-685.

Otsuka

AVANIR pharmaceuticals

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NUEDEXTA® (dextromethorphan HBr and quinidine sulfate) Capsules 20mg/10mg

Brief Summary of Prescribing Information
See package insert for full Prescribing Information

INDICATIONS AND USAGE
NUEDEXTA is indicated for the treatment of pseudobulbar affect (PBA). PBA occurs secondary to a variety of otherwise unrelated neurologic conditions, and is characterized by involuntary, sudden, and frequent episodes of laughing and/or crying. PBA episodes typically occur out of proportion or incongruent to the underlying emotional state. PBA is a specific condition, distinct from other types of emotional lability that may occur in patients with neurological disease or injury.

DOSAGE AND ADMINISTRATION
The recommended starting dose of NUEDEXTA (20 mg dextromethorphan hydrobromide and 10 mg quinidine sulfate) is one capsule daily by mouth for the initial seven days of therapy. On the eighth day of therapy and thereafter, the daily dose should be a total of two capsules a day, given as one capsule every 12 hours. The need for continued treatment should be reassessed periodically, as spontaneous improvement of PBA occurs in some patients.

CONTRAINDICATIONS
Quinidine and related drugs: NUEDEXTA contains quinidine, and should not be used concomitantly with other drugs containing quinidine, quinine, or mefloquine. **Hypersensitivity:** NUEDEXTA is contraindicated in patients with a history of NUEDEXTA, quinine, mefloquine or quinidine-induced thrombocytopenia, hepatitis, bone marrow depression or lupus-like syndrome; also in patients with known hypersensitivity to dextromethorphan *[see Warnings and Precautions (5.1 in full PI)]*. **MAOIs:** NUEDEXTA is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious and possibly fatal drug interactions, including serotonin syndrome. Allow at least 14 days after stopping NUEDEXTA before starting an MAOI *[see Drug Interactions (7.1 in full PI)]*. **Cardiovascular:** NUEDEXTA is contraindicated in patients with a prolonged QT interval, congenital long QT syndrome or a history suggestive of torsades de pointes, and in patients with heart failure *[see Warnings and Precautions (5.3 in full PI)]*. NUEDEXTA is contraindicated in patients receiving drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine and pimozide), as effects on QT interval may be increased *[see Drug Interactions (7.2 in full PI)]*. NUEDEXTA is contraindicated in patients with complete atrioventricular (AV) block without implanted pacemakers, or in patients who are at high risk of complete AV block.

WARNINGS AND PRECAUTIONS
Thrombocytopenia and Other Hypersensitivity Reactions: Quinidine can cause immune-mediated thrombocytopenia that can be severe or fatal. Non-specific symptoms, such as lightheadedness, chills, fever, nausea, and vomiting, can precede or occur with thrombocytopenia. NUEDEXTA should be discontinued immediately if thrombocytopenia occurs, unless the thrombocytopenia is not drug-related, as continued use increases the risk for fatal hemorrhage. Likewise, NUEDEXTA should not be restarted in sensitized patients, because of the risk of more rapid and more severe thrombocytopenia. NUEDEXTA should not be used if immune-mediated thrombocytopenia from structurally related drugs including quinine and mefloquine is suspected, as cross-sensitivity can occur. Quinidine-associated thrombocytopenia usually resolves within a few days of discontinuation of the sensitizing drug. Quinidine has also been associated with a lupus-like syndrome involving polyarthritis, sometimes with a positive ANA. Other associations include rash, bronchospasm, adenopathy, hemolytic anemia, vasculitis, uveitis, angioedema, agranulocytosis, the sicca syndrome, myalgia, elevated serum levels of skeletal muscle enzymes, and pneumonitis. **Hepatotoxicity:** Hepatitis has been reported in patients receiving quinidine, generally during the first few weeks of therapy. **Cardiac Effects:** NUEDEXTA causes dose-dependent QTc prolongation *[see Clinical Pharmacology (12.2 in full PI)]*. QT prolongation can cause torsades de pointes-type ventricular tachycardia, with the risk increasing as prolongation increases. When initiating NUEDEXTA in at risk patients, ECG evaluation of QT interval should be done at baseline and 3-4 hours after the first dose. This includes patients concomitantly taking drugs that prolong the QT interval or that are strong or moderate CYP3A4 inhibitors, and patients with left ventricular hypertrophy (LVH) or left ventricular dysfunction (LVD). LVH and LVD are more likely to be present in patients with chronic hypertension, known coronary artery disease, or history of stroke. LVH and LVD can be diagnosed utilizing echocardiography or another suitable cardiac imaging modality. Reevaluate ECG if risk factors for arrhythmia change during the course of treatment. Risk factors include concomitant use of drugs associated with QT prolongation, electrolyte abnormality (hypokalemia, hypomagnesemia), bradycardia, and family history of QT abnormality. Hypokalemia and hypomagnesemia should be corrected prior to initiation of therapy with NUEDEXTA, and should be monitored during treatment. If patients experience symptoms that could indicate cardiac arrhythmias, e.g., syncope or palpitations, NUEDEXTA should be discontinued and the patient further evaluated. **Concomitant use of CYP2D6 Substrates:** The quinidine in NUEDEXTA inhibits CYP2D6 in patients in whom CYP2D6 is not otherwise genetically absent or its activity otherwise pharmacologically inhibited *[see CYP2D6 Poor Metabolizers (5.8 in full PI), Pharmacokinetics (12.3 in full PI), Pharmacogenomics (12.5 in full PI)]*. Because of this effect on CYP2D6, accumulation of parent drug and/or failure of active metabolite formation may decrease the safety and/or the efficacy of drugs used concomitantly with NUEDEXTA that are metabolized by CYP2D6 *[see Drug Interactions (7.5 in full PI)]*. **Dizziness:** In a controlled trial of NUEDEXTA, 10% of patients on NUEDEXTA and 5% on placebo experienced dizziness. **Serotonin Syndrome:** When used with SSRIs or tricyclic antidepressants, NUEDEXTA may cause serotonin syndrome, including altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor *[see Drug Interactions (7.4 in full PI), Overdosage (10 in full PI)]*. **Anticholinergic Effects of Quinidine:** Monitor for worsening clinical condition in diseases that may be adversely affected by anticholinergic effects. **CYP2D6 Poor Metabolizers:** The quinidine component of NUEDEXTA is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared to when dextromethorphan is given alone *[see Concomitant use of CYP2D6 substrates (5.4 in full PI), Pharmacokinetics (12.3 in full PI), Pharmacogenomics (12.5 in full PI)]*. Approximately 7-10% of Caucasians and 3-8% of African Americans are poor metabolizers (PMs) lacking capacity to metabolize CYP2D6. In patients who may be at risk of significant toxicity due to quinidine, consider genotyping to determine if they are PMs prior to treating with NUEDEXTA.

ADVERSE REACTIONS
A total of 946 patients participated in four Phase 3 controlled and uncontrolled PBA studies and received at least one dose of the combination product of dextromethorphan hydrobromide/quinidine sulfate in various strengths at the recommended or higher than the recommended dose. In a 12-week, placebo-controlled study (N=326), the most commonly reported adverse reactions (incidence ≥ 2% and greater than placebo) that led to discontinuation were muscle spasticity (3%), respiratory failure (1%), abdominal pain (2%), asthenia (2%), dizziness (2%), fall (1%), and muscle spasms (2%). The most common adverse reactions (≥ 3% and ≥ 2X placebo) were diarrhea (13%), dizziness (10%), cough (5%), vomiting (5%), asthenia (5%), edema (5%), urinary tract infection (4%), influenza (4%), flatulence (3%) and increased GGT (3%). Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. **Safety Experience of Individual Components:** *Dextromethorphan:* Drowsiness, dizziness, nervousness or restlessness, nausea, vomiting, and stomach pain. *Quinidine:* Cinchonism (nausea, vomiting, diarrhea, headache, tinnitus, hearing loss, vertigo, blurred vision, diplopia, photophobia, confusion, and delirium) is most often a sign of chronic quinidine toxicity, but it may appear in sensitive patients after a single moderate dose of several hundred milligrams. Other adverse reactions occasionally reported with quinidine therapy include depression, mydriasis, disturbed color perception, night blindness, scotomata, optic neuritis, visual field loss, photosensitivity, keratopathy, and abnormalities of skin pigmentation.

DRUG INTERACTIONS
MAOIs: Do not use NUEDEXTA with monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding or following 14 days *[see Contraindications (4.3 in full PI)]*. **Drugs that Prolong QT and are Metabolized by CYP2D6:** Do not use with drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine or pimozide) *[see Contraindications (4.4 in full PI)]*. **Drugs that Prolong QT and Concomitant CYP3A4 Inhibitors:** Recommend ECG in these patients who are taking NUEDEXTA *[see Warnings and Precautions (5.3 in full PI)]*. **SSRIs and Tricyclic Antidepressants:** Use of NUEDEXTA with SSRIs or tricyclic antidepressants increases the risk of serotonin syndrome *[see Warnings and Precautions (5.6 in full PI)]*. **CYP2D6 Substrate:** The co-administration of NUEDEXTA with drugs that undergo extensive CYP2D6 metabolism may result in altered drug effects *[see Warnings and Precautions (5.4 in full PI)]*. ***Desipramine (CYP2D6 substrate):*** This tricyclic antidepressant is metabolized primarily by CYP2D6. A drug interaction study was conducted between a higher combination dose of dextromethorphan (dextromethorphan hydrobromide 30 mg/quinidine sulfate 30 mg) and desipramine 25 mg. This dose increased steady state desipramine levels approximately 8-fold. If NUEDEXTA and desipramine are prescribed concomitantly, the initial dose of desipramine should be markedly reduced. The dose of desipramine can then be adjusted based on response, but a dose above 40 mg/day is not recommended. ***Paroxetine (CYP2D6 inhibitor and substrate):*** When the combination dose of dextromethorphan hydrobromide 30 mg/quinidine sulfate 30 mg was added to paroxetine at steady state, paroxetine exposure ($AUC_{0\text{-}24}$) increased by 1.7 fold and C_{max} increased by 1.5 fold. Consider initiating treatment with a lower dose of paroxetine if given with NUEDEXTA. The dose of paroxetine can then be adjusted based on response, but dosage above 35 mg/day is not recommended. **Digoxin:** Quinidine is an inhibitor of P-glycoprotein. Prescribing quinidine with digoxin, a P-glycoprotein substrate, results in serum digoxin levels that may be as much as doubled. **Alcohol:** As with any other CNS drug, caution should be used when NUEDEXTA is taken in combination with other centrally acting drugs and alcohol.

USE IN SPECIFIC POPULATIONS
Pregnancy Category C: There are no adequate studies of NUEDEXTA in pregnant women *[see Pregnancy (8.1 in full PI)]*. **Labor and Delivery:** The effects of NUEDEXTA on labor and delivery are unknown. **Nursing Mothers:** It is not known whether dextromethorphan and/or quinidine are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NUEDEXTA is given to a nursing mother. **Pediatric and Geriatric Use:** The safety and effectiveness of NUEDEXTA in these populations has not been determined. **Renal and Hepatic Impairment:** Dose adjustment of NUEDEXTA is not required in patients with mild to moderate renal or hepatic impairment. Increases in dextromethorphan and/or quinidine levels are likely to be observed in patients with severe renal or hepatic impairment.

DRUG ABUSE AND DEPENDENCE
NUEDEXTA contains dextromethorphan, and dextromethorphan abuse has been reported, predominately in adolescents. These observations were not systematic and it is not possible to predict on the basis of this experience the extent to which NUEDEXTA will be misused once marketed. Therefore, patients with a history of drug abuse should be observed closely.

OVERDOSAGE
Evaluation and treatment of NUEDEXTA overdose is based on experience with the individual components. Treatment of dextromethorphan overdosage should be directed at symptomatic and supportive measures. Treatment of quinidine overdosage requires monitoring the QTc interval and should involve a healthcare provider experienced in cardiac arrhythmia prevention and treatment and α-blockade-induced hypotension. Because of the theoretical possibility of QT prolongation that might be additive to those of quinidine, antiarrhythmics with Class I (procainamide) or Class III activities should (if possible) be avoided.

PATIENT COUNSELING INFORMATION
Physicians should discuss the following topics with patients when prescribing NUEDEXTA: **Hypersensitivity:** *[see Contraindications (4.2 in full PI), Warnings and Precautions (5.1 in full PI)]*. **Cardiac effects:** Consult their healthcare provider immediately if they feel faint or lose consciousness. Inform their healthcare provider if they have any personal or family history of QTc prolongation *[see Contraindications (4.4 in full PI), Warnings and Precautions (5.3 in full PI) Drug Interactions (7 in full PI)]*. **Dizziness:** *[see Warnings and Precautions (5.5 in full PI), Adverse Reactions (6.1 in full PI)]*. **Drug Interactions:** *[see Drug Interactions (7 in full PI)]*. **Dosing:** Instruct patients to take NUEDEXTA exactly as prescribed, not to take more than 2 capsules in a 24-hour period, to be sure that there is an approximate 12-hour interval between doses, and not to take a double dose after a missed dose. **General:** Contact their healthcare provider if their PBA symptoms persist or worsen. Advise patients to keep this and all medications out of reach of children and pets.

Marketed by Avanir Pharmaceuticals, Inc., Aliso Viejo, CA 92656
1-855-4NUEDEX (468-3339)
www.NUEDEXTA.com

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AVANIR® pharmaceuticals

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CNS SPECTRUMS

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Cover Image: The image on the cover shows a hypothetical model whereby glutamate is released from an intracortical pyramidal neuron and binds to an NMDA receptor on a GABA-ergic interneuron. GABA is then released and binds to receptors on the axon of another glutamate pyramidal neuron. This inhibits the neuron, thus reducing the release of cortical glutamate. The GABA interneuron and its NMDA synapse from the first neuron to the second is the hypothetical site of glutamate dysfunction in schizophrenia.

Stahl's Essential Psychopharmacology, 4th edition, by Stephen M. Stahl

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Aims and Scope

CNS Spectrums aims to be the premiere journal covering all aspects of clinical neurosciences, neurotherapeutics and neurospsychopharmacology. From 2012 the journal will primarily focus on the publication of authoritative, cross-disciplinary review and opinion material publishing advances and controversial issues with pertinence to the clinician. In particular we aim to publish reviews and articles in translational neuroscience, biological psychiatry and neuropsychopharmacology that explain clinically relevant neuroscience discoveries in a way that makes these findings accessible and understandable to clinicians and clinical investigators. We will emphasize new therapeutics of all types in clinical neurosciences, mental health, psychiatry, and neurology, especially first in man studies and proof of concept studies. Our focus will be not just drugs, but novel psychotherapies and neurostimulation therapeutics as well. *CNS Spectrums* will in addition, continue to publish original research and commentaries that focus on emergent areas of research. Subject coverage shall span the full spectrum of neuropsychiatry focusing on translational issues and those crossing traditional boundaries between neurology and psychiatry.

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