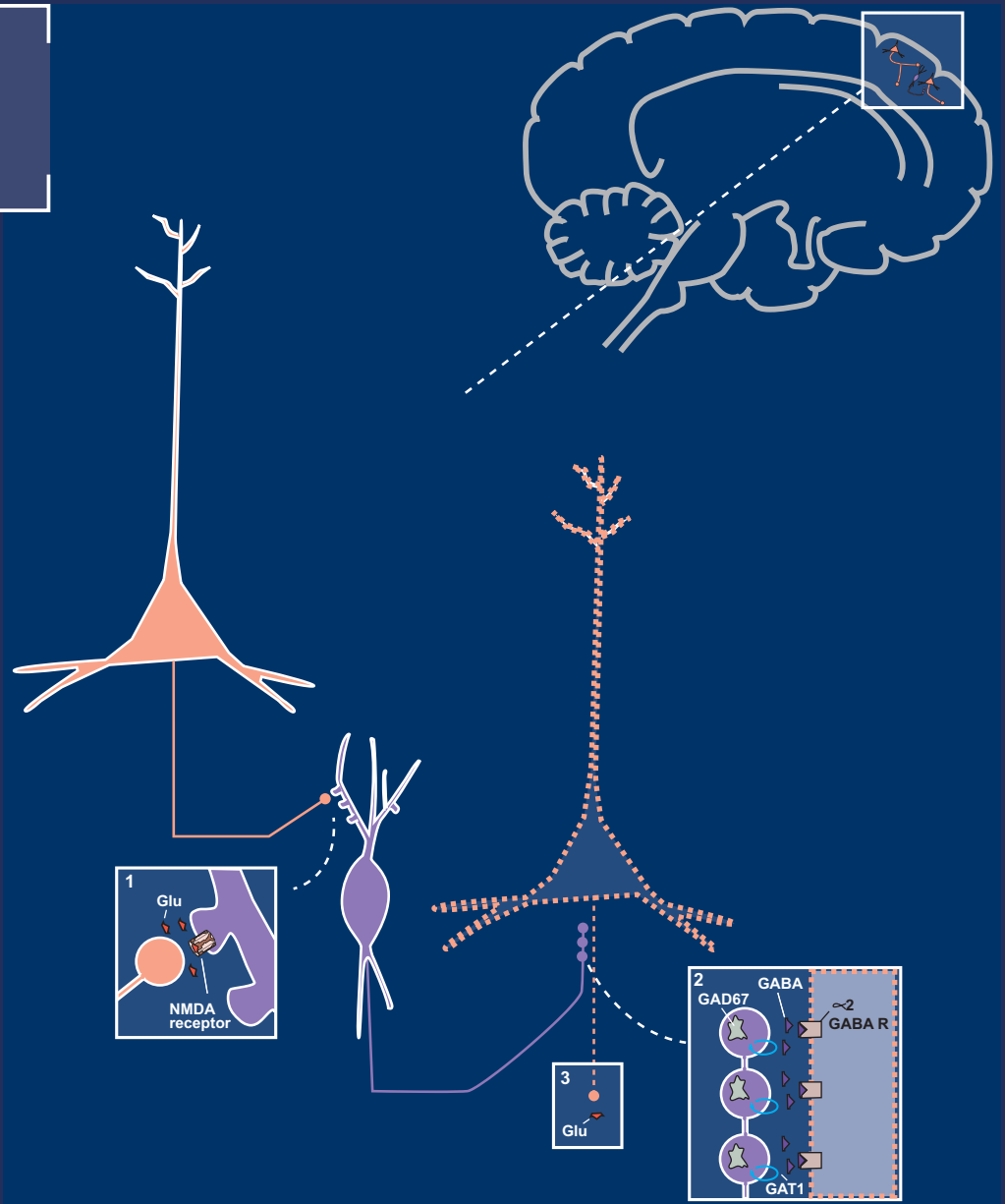


VOLUME 21 | ISSUE 2

April 2016

ISSN: 1092-8529



journals.cambridge.org/cns

CNS SPECTRUMS

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



The journal of the
**Neuroscience
Education Institute**

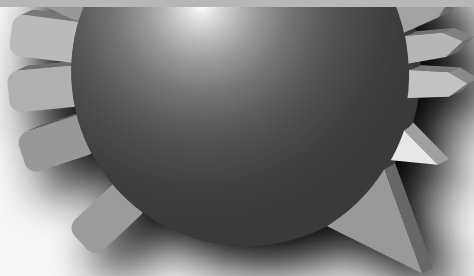


**CAMBRIDGE
UNIVERSITY PRESS**

Want some CME with that?

STAHL

MASTERCLASS



- An online educational program in core areas of psychiatry with interactive readings, short lectures, animations and case studies

- Self-testing and opportunities to claim formal CME credits, all taken at a self-directed speed

- Written and moderated by experts in the field from the Dr. Stahl's Neuroscience Education Institute and the University of Cambridge

For more information, please go to
www.stahlmasterclass.com



CAMBRIDGE
UNIVERSITY PRESS

Case Studies: Stahl's Essential Psychopharmacology

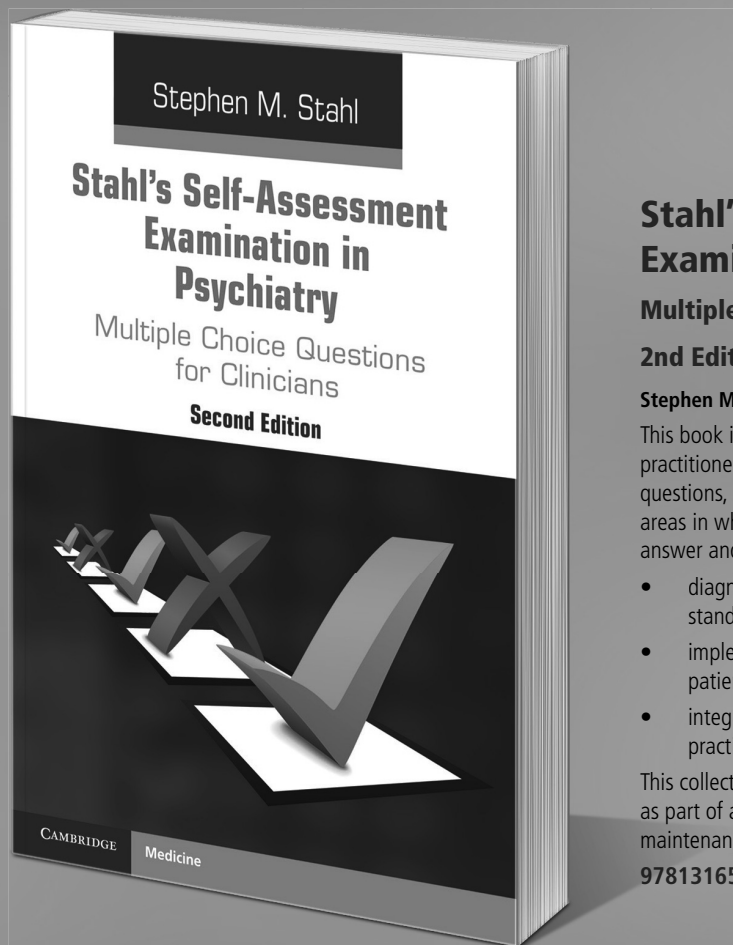
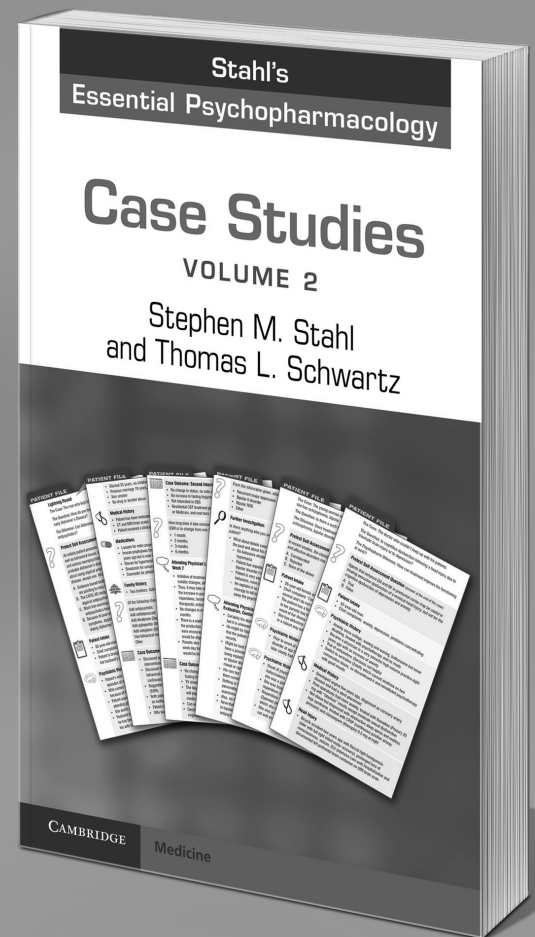
Volume 2

Stephen M. Stahl, *Neuroscience Education Institute*

Thomas L. Schwartz, *SUNY Upstate Medical University*

Following the success of the first collection of Stahl's Case Studies, published in 2011, we are pleased to present this completely new selection of clinical stories. Designed with the distinctive user-friendly presentation readers have become accustomed to and making use of icons, questions/answers and tips, these cases address complex issues in an understandable way and with direct relevance to the everyday experience of clinicians. Covering a wide-ranging and representative selection of clinical scenarios, each case is followed through the complete clinical encounter, from start to resolution, acknowledging all the complications, issues, decisions, twists and turns along the way. The book is about living through the treatments that work, the treatments that fail, and the mistakes made along the journey. This is psychiatry in real life - these are the patients from your waiting room - this book will reassure, inform and guide better clinical decision making.

9781107607330 / Paperback / March 2016 / \$79.99 / £49.99



Stahl's Self-Assessment Examination in Psychiatry

Multiple Choice Questions for Clinicians

2nd Edition

Stephen M. Stahl, *Neuroscience Education Institute*

This book is for prescribers specializing in psychiatry, primary care physicians, nurse practitioners, psychologists and pharmacists. Featuring 150 new and updated case-based questions, divided into ten core areas of psychiatry, this collection will help you identify areas in which you need further study. Each question is followed by an explanation of the answer and a list of references. After completing the questions you will be better able to:

- diagnose patients presenting with psychiatric symptoms using accepted diagnostic standards and practices
- implement evidence-based psychiatric treatment strategies aligned with the patient's recovery goals
- integrate recent advances in diagnostic and treatment strategies into clinical practice according to best practice guidelines.

This collection has been approved by the American Board of Psychiatry and Neurology as part of a lifelong learning and self-assessment program and as a component of maintenance of certification.

9781316502495 / Paperback / January 2016 / \$59.99 / £39.99

For more information, please go to
www.cambridge.org



CAMBRIDGE
UNIVERSITY PRESS



NUEDEXTA[®]

(dextromethorphan HBr and quinidine sulfate) capsules **20 mg**
10 mg

APPROVED SINCE

2010¹

Over 1,000,000 prescriptions*

*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 PBA¹

PBA is often mischaracterized as depression⁴⁻⁶

**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?

^dA 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 pimozone); 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.

^bWhen 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

^cIn 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. Crumacker 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.

©2016 Avanir Pharmaceuticals, Inc. All rights reserved. NUE-0101-ADV-0116



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 polyarthritides, 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 $\geq 2\%$ 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 ($\geq 3\%$ and $\geq 2\times$ 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 (AUC₀₋₂₄) 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, predominantly 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 overdose should be directed at symptomatic and supportive measures. Treatment of quinidine overdose 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)].
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
© 2015 Avanir Pharmaceuticals, Inc.

NUE-0016(1)-OTH-0715



CNS SPECTRUMS

CONTENTS

BRAINSTORMS

- Mechanism of action of cariprazine**
Stephen M. Stahl 123

EDITORIAL

- Psychiatry and terrorism: exploring the unacceptable**
Donatella Marazziti 128

- Adult autism spectrum as a transnosographic dimension**
Liliana Dell'Osso, Riccardo Dalle Luche and Mario Maj 131

REVIEW ARTICLE

- Psychopharmacological options for adult patients with anorexia nervosa**
Mario Miniati, Mauro Mauri, Agnese Ciberti, Michela Giorgi Mariani, Donatella Marazziti and Liliana Dell'Osso 134

- Effects of serotonin in the hippocampus: how SSRIs and multimodal antidepressants might regulate pyramidal cell function**
Elena Dale, Alan L. Pehrson, Theepica Jeyarajah, Yan Li, Steven C. Leiser, Gennady Smagin, Christina K. Olsen and Connie Sanchez 143

- Regional distribution of serotonergic receptors: a systems neuroscience perspective on the downstream effects of the multimodal-acting antidepressant vortioxetine on excitatory and inhibitory neurotransmission**
Alan L. Pehrson, Theepica Jeyarajah and Connie Sanchez 162

- Comorbidity between depression and inflammatory bowel disease explained by immune-inflammatory, oxidative, and nitrosative stress; tryptophan catabolite; and gut-brain pathways**
Marta Martin-Subero, George Anderson, Buranee Kanchanatawan, Michael Berk and Michael Maes 184

ORIGINAL RESEARCH

- Psychometric evaluation of the Work Readiness Questionnaire in schizophrenia**
Steven G. Potkin, Dragana Bugarski-Kirola, Chris J. Edgar, Sherif Soliman, Stephanie Le Scouiller, Jelena Kunovac, Eugenio Miguel Velasco and George M. Garibaldi 199

- Addictive behaviors and personality traits in adolescents**
Donato Munno, Marta Saroldi, Elisa Bechon, Sara Chiara Maria Sterpone and Giuseppina Zullo 207

Editor-in-Chief

Stephen M. Stahl, Adjunct Professor of Psychiatry at the University of California San Diego, USA;
Honorary Visiting Senior Fellow at the University of Cambridge, UK.

Field Editors

Joseph F. Goldberg, Icahn School of Medicine at Mount Sinai, USA
Thomas E. Schlaepfer, University Hospital Bonn, Germany
Frank I. Tarazi, Harvard Medical School, USA
Carlos A. Zarate, National Institute of Mental Health, USA

Deputy Editor

Thomas L. Schwartz, SUNY Upstate Medical University at Syracuse, USA

Editorial Board

Dennis S. Charney, Mount Sinai School of Medicine, USA
Maria Conceição do Rosario, University of São Paulo Medical School, Brazil
Jeffrey L. Cummings, Cleveland Clinic, USA
Thilo Deckersbach, Harvard Medical School, USA
Koen Demyttenaere, University Psychiatric Center KuLeuven, Belgium
Karen D. Ersche, University of Cambridge, UK
Robert L. Findling, The Johns Hopkins Hospital, USA
Patrick R. Finley, University of California, San Francisco, USA
Mark S. George, Medical University of South Carolina, USA
Ira D. Glick, Stanford University, USA
Joseph F. Goldberg, Icahn School of Medicine at Mount Sinai, USA
Eric Hollander, Albert Einstein College of Medicine and Montefiore Medical Center, USA
Daphne Holt, Harvard Medical School, USA
Peter B. Jones, University of Cambridge, UK
Andres M. Kanner, University of Miami, USA
Antony D. Loebel, New York University School of Medicine, USA
Donatella Marazziti, University of Pisa, Italy
Herbert Y. Meltzer, Northwestern University, USA
Philip Mitchell, University of New South Wales, Australia
Jun Nakamura, University of Occupational and Environmental Health, Japan
Humberto Nicolini, National Institutes of Health, Minister of Health, México
Andrew A. Nierenberg, Harvard Medical School, USA
Stefano Pallanti, University of Florence, Italy
Katharine A. Phillips, Brown University, USA
Diego A. Pizzagalli, Harvard Medical School, USA
Mark H. Pollack, Rush University Medical Center, USA
Mark H. Rapaport, Emory University, USA
Irismar Reis de Oliveira, Universidade Federal da Bahia, Brazil
Trevor W. Robbins, University of Cambridge, UK
Peter P. Roy-Byrne, University of Washington School of Medicine, USA
Barbara J. Sahakian, University of Cambridge, UK
Gerard Sanacora, Yale University School of Medicine, USA
Alan F. Schatzberg, Stanford University School of Medicine, USA
Thomas E. Schlaepfer, University of Bonn, Germany
Thomas L. Schwartz, SUNY Upstate Medical University in Syracuse, USA
Jordan W. Smoller, Harvard Medical School, USA
Dan J. Stein, University of Cape Town (UCT), South Africa
Stephen Strakowski, University of Cincinnati, USA
T. Scott Stroup, Columbia University, USA
Frank I. Tarazi, Harvard Medical School, USA
Michael E. Thase, University of Pennsylvania, USA
Michael Trimble, National Hospital for Neurology, Queen Square, London
Madhukar H. Trivedi, University of Texas Southwestern Medical Center, USA
Karen Dineen Wagner, The University of Texas Medical Branch, USA
Katherine D. Warburton, California Department of State Hospitals, USA
Stephen R. Wisniewski, University of Pittsburgh, USA
Shigeto Yamawaki, Hiroshima University, Japan
Carlos A. Zarate, Jr., National Institute of Mental Health, USA
Joseph Zohar, Tel Aviv University, Israel

Managing Editor

Lisa Arrington, Cambridge University Press (larrington@cambridge.org)

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

Copyright © 2016 Stephen M. Stahl. Reproduced with permission.

Aims and Scope

CNS Spectrums aims to be the premiere journal covering all aspects of clinical neurosciences, neurotherapeutics and neuropsychopharmacology. 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.

Submitting Manuscripts to *CNS Spectrums*

All submissions to *CNS Spectrums* should be prepared in accordance with the instructions for authors and in the style of the Journal. Manuscripts should be submitted through the dedicated *CNS Spectrums* ScholarOne Manuscripts website: <http://mc.manuscriptcentral.com/cnsspectr>

CNS Spectrums will consider and encourage the following types of articles for publication: **Review Article**—Comprehensive article summarizing and synthesizing the literature on various topics presented in a scholarly and clinically relevant fashion; **Original Research**—Reports the results of a clinical study and contains original research; **Opinion**—Address a current topic of high interest, which has substantial evidence but has not yet been established; **Commentary**—An article that is written in reaction to previously published articles; usually encouraging a level of debate; the journal will also include **Brainstorms** and **Editorials** that shall be commissioned or written by the Editor-in-Chief.

Instructions for Contributors

The Instructions for Contributors are available on the Cambridge Journals Online web site at: <http://journals.cambridge.org/CNSifc>

Indexing

CNS Spectrums is indexed by *Index Medicus*/MEDLINE and Web of Science (Thomson Reuters) as well as appearing in the annual Journal Citation Report. Introduced in 1996, the journal was acquired in whole by Cambridge University Press in November of 2011.

Subscriptions

Institutional print and electronic: £544/\$862; Institutional electronic only: £413/\$660.

© Cambridge University Press 2016. All rights reserved.

No part of this publication may be reproduced, in any form or by any means, electronic, photocopying, or otherwise, without permission in writing from Cambridge University Press. Policies, request forms, and contacts are available at: <http://www.cambridge.org/rights/permissions/permission.htm>. Permission to copy (for users in the U.S.A.) is available from Copyright Clearance Center <http://www.copyright.com>, email: info@copyright.com.

Rights & permissions requests can be applied for online within each article by clicking "Request Permissions" within the table of contents or in the fulltext version of a specific article. Requests will be processed via the CCC Rightslink system and processed immediately.

CNS Spectrums (ISSN: Print 1092-8529; eISSN: 2165-6509) is published bimonthly by Cambridge University Press.

Postmaster

Send address changes in the U.S.A., Canada, and Mexico to *CNS Spectrums*, Cambridge University Press, Journals Dept., 32 Avenue of the Americas, New York, NY 10013-2412, U.S.A. Send address changes elsewhere to *CNS Spectrums*, Cambridge University Press, The Edinburgh Building, Shaftesbury Road, Cambridge CB2 8RU, England.

Online availability

CNS Spectrums is hosted on the Cambridge Journals Online (CJO) service at <http://journals.cambridge.org/cns>

Institutional subscribers: Access to full-text articles online is only granted to subscription options offering an online component. Subscriptions must be activated by the purchasing institution using the instructions provided at the time of purchase; see information for subscribers at: <http://journals.cambridge.org/>

Reprint and Advertising Sales

Inquiries for bulk reprint sales should be sent to USReprints@cambridge.org. Advertising inquiries should be sent to M. J. Mrvica Associates, Inc., 2 West Taunton Avenue, Berlin, NJ 08009; Phone: 856-768-9360; Fax: 856-753-0064; Email: mjmrvica@mrvica.com.