SYLLABUS AND COURSE GUIDE

Session I: Tuesday, July 11, 2017
Session II: Thursday, July 13, 2017

WC-034-071117-03
WC-035-071317-03

Four-Part Case Series: Treatment Challenges in Schizophrenia - *Q&A Session I & II*

FACULTY: John M. Kane, MD

neuroscience CME

A Free, 30 Minute CME/CPE LIVE Q&A Case Based Session
Tuesday, July 11, 2017, at 12:00 PM ET (Session I) OR
Thursday, July 13, 2017, at 3:00 PM ET (Session II)

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INFORMATION FOR PARTICIPANTS

Statement of Need

The positive symptoms of schizophrenia, such as hallucinations, delusions, and aggressive symptoms, receive the most clinical attention and are the primary targets for pharmacological treatment. Unfortunately, it is the negative and cognitive symptoms that persist longer than positive symptoms, are more difficult to treat, and contribute to chronicity and disability.[1]

The newer treatments that have become available are better tolerated with improved side-effect profiles and may have an important role in improving social functioning. There has been an unmet need for better tolerated antipsychotics with broad-based symptom control that improve patient functioning. Recently, FDA-approved agents that offer partial D2 receptor agonism and have other unique properties that may affect the clinical profile offer the possibility of improved symptom management and reduced adverse effects.

In this CME Outfitters patient case and expert consult Q & A session, faculty will go in-depth with the case study answering your questions while offering evidence, guidelines, and quality measures to improve the long term management of patients with schizophrenia.

1. Roberts RJ, Findlay LJ, El-Mallakh PL, El-Mallakh RS. Update on schizophrenia and bipolar disorder: focus on cariprazine. *Neuropsychiatr Dis Treat*. 2016;12:1837-1842.

Learning Objectives

At the end of this CE activity, participants should be able to:

- Evaluate the efficacy and safety profiles of recent FDA-approved agents to treat schizophrenia for inclusion into appropriate treatment plans.
- Incorporate into practice the latest advances in the management of schizophrenia.

Target Audience

Psychiatrists, pharmacists, and other members of the interprofessional team caring for individuals with schizophrenia.

Financial Support

Supported by an educational grant from Allergan.

CREDIT INFORMATION

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Universal Activity Number Session I: 0376-0000-17-023-L01-P (live program)
0376-0000-17-023-H01-P (recorded program)

Universal Activity Number Session II: 0376-0000-17-024-L01-P (live program)
0376-0000-17-024-H01-P (recorded program)

Type: knowledge-based

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There is no fee for participation in this activity. The estimated time for completion is 30 minutes.
Questions? Please call **877.CME.PROS**.

FACULTY BIOS & DISCLOSURES

John M. Kane, MD

Dr. Kane is Senior Vice President for Behavioral Health Services at Northwell Health in New Hyde Park, New York. He is Professor and Chairman of Psychiatry at The Hofstra Northwell School of Medicine. He also serves as Chairman of Psychiatry at The Zucker Hillside Hospital in Glen Oaks, New York. Dr. Kane earned his medical degree from New York University in New York, New York, and completed his internship and residency in Psychiatry at The Zucker Hillside Hospital. He is a Diplomate of the American Board of Psychiatry and Neurology.

Dr. Kane is the recipient of many awards, including: the Lieber Prize; The APA's Kempf Award, the Gralnick Award and Foundations Prize; the New York State Office of Mental Health Lifetime Achievement Award; and The Dean Award from the American College of Psychiatrists. He has served as President of the American Society of Clinical Psychopharmacology, the Psychiatry Research Society and the Schizophrenia International Research Society. Dr. Kane has been the principal investigator for research projects focusing on schizophrenia psychobiology, treatment and recovery, as well as improving quality and cost of care. He is the author of over 400 peer-reviewed papers and serves on the editorial boards of numerous journals.

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Dr. Kane has disclosed that he receives grant support from Janssen Pharmaceuticals Inc. and Otsuka. He serves on the advisory board for Alkermes; Intra-Cellular Therapies, Inc.; Lundbeck; Neurocrine Biosciences Inc.; Otsuka America Pharmaceutical, Inc.; Pierre Fabre; Takeda Pharmaceuticals U.S.A., Inc.; and Teva. He serves as a consultant for Alkermes; Allergan; Eli Lilly and Company; Forum Pharmaceuticals Inc.; Genentech, Inc.; Intra-Cellular Therapies, Inc.; Janssen Pharmaceuticals, Inc.; Johnson & Johnson; Lundbeck; Neurocrine Biosciences Inc.; Otsuka America Pharmaceutical, Inc.; Pierre Fabre; Reviva Pharmaceuticals Inc.; Roche; Sunovion Pharmaceuticals Inc.; Takeda Pharmaceuticals U.S.A., Inc.; and Teva. He is a shareholder of LB Pharmaceuticals Inc.; MedAvante Inc.; and Vanguard Research Group.

Tony Graham, MD (peer reviewer) has no disclosures to report.

Kashemi D. Rorie, PhD (planning committee) has no disclosures to report.

Sharon Tordoff, CHCP (planning committee) has no disclosures to report.

Jan Perez, CHCP (planning committee) has no disclosures to report.

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Four-Part Case Series:
Treatment Challenges in Schizophrenia
Q&A Sessions 1 & 2

Supported by an educational grant from Allergan.

John M. Kane, MD

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Professor and Chair, Department of Psychiatry
Hofstra Northwell School of Medicine
Hempstead, NY

Learning Objective 1

Evaluate the efficacy and safety profiles of recent FDA-approved agents to treat schizophrenia for inclusion into appropriate treatment plans.

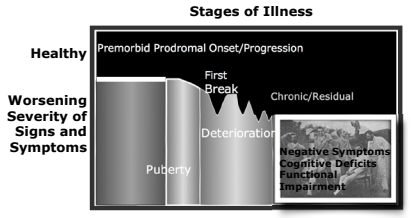
Learning Objective 2

Incorporate into practice the latest advances in the management of schizophrenia.

Revisiting the Case of TC

- TC is a 24-year-old man who has had two hospitalizations for psychosis
- He first became ill at the age of 19
- Though his psychotic symptoms are largely under control, he shows little motivation

Natural History of Schizophrenia: Rationale for Early Detection and Intervention



Lieberman JA, et al. Biol Psychiatry. 2001;50(11):884-897.

Diagnostic Considerations for TC

- Confirming his diagnosis
- Differentiating schizophrenia from other conditions that mimic schizophrenia
- Course of Illness
- Family history
- Medical and/or psychiatric comorbidities

Treatment Goals for Schizophrenia: APA Guidelines

Acute Phase
- Prevent harm to self or others
- Control disturbed behavior
- Reduce severity of psychosis
- Address precipitating factors
- Return to best level of functioning
- Develop alliance with patient and family
- Formulate treatment plan
- Facilitate aftercare

Stabilization Phase
- Reduce stress on patient
- Minimize likelihood of relapse
- Enhance adaptation to life in community
- Facilitate symptom reduction and remission
- Promote recovery

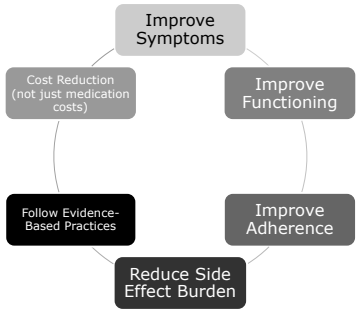
Stable Phase
- Sustain symptom remission or control
- Ensure maintenance or continued improvement of functioning and QoL
- Treat exacerbation of symptoms or relapses
- Monitor for adverse treatment effects

American Psychiatric Association. Available at http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/schizophrenia.pdf. Accessed June 29, 2017.

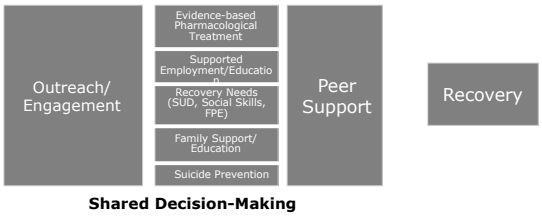
Revisiting the Case of TC

- His family is exasperated and does not know how hard to push or encourage him.

Best Practices for Recovery



Connection Team Interventions



National Institute of Mental Health. Available at https://www.nimh.nih.gov/health/topics/schizophrenia/raise/state-health-administrators-and-clinics.shtml. Accessed June 29, 2017.

Revisiting the Case of TC

- He has not responded to a trial of antidepressants

FDA-Approved Antipsychotics

- Chlorpromazine - 1957
- Perphenazine - 1957
- Trifluoperazine - 1959
- Fluphenazine* - 1960
- Thioridazine - 1962
- Haloperidol* - 1967
- Thiothixene - 1967
- Molindone - 1974
- Loxapine - 1975
- Pimozide - 1984
- Clozapine -1989
- Risperidone* - 1993
- Olanzapine* - 1996
- Quetiapine - 1997
- Ziprasidone - 2001
- Aripiprazole* - 2002
- Paliperidone* - 2006
- Iloperidone - 2009
- Asenapine - 2009
- Lurasidone - 2010
- Brexpiprazole - 2015
- Cariprazine - 2015
- Pimavanserin** - 2016

*Has long-acting injectable formulation; **Not FDA-approved for schizophrenia
[Package Insert]. Drugs@FDA Website.

Nonpharmacological Treatments

- Cognitive Remediation Therapy
  - Helps to improve cognitive deficits
- Cognitive Adaptation Training
  - Helps bypass cognitive deficits
- Cognitive Behavioral Therapy
  - Psychotherapy to target symptoms; durable over time
- Individual Placement and Supported Employment
  - Help patient get into competitive job they would like to do

Fredrick MM, et al. *Schizophr Res.* 2015 Aug;166(1-3):290-6; Patel KR, et al. *P T.* 2014 Sep; 39(9): 638–645; Barlati S, et al. *Schizophr Res Treatment.* 2013;2013:156084.

The Do's and Don'ts of Managing Patients Like TC

- Dosing/titration
- Switching
- Adjunctive therapy
- Initial treatment considerations
- Patient follow-up intervals
- Management of comorbidities
- Shared decision-making

SMART Goals:
Managing Patients Like TC

- Recovery, not just symptomatic remission, should be the goal of therapy
- Accurately diagnose schizophrenia; differential diagnosis is critical
- Identifying appropriate therapy includes:
  - utilizing evidence-based strategies
  - considering safety and tolerability profiles of agents
  - understanding patient preferences
  - monitoring treatment outcomes

Questions & Answers

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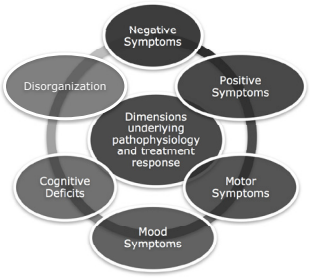
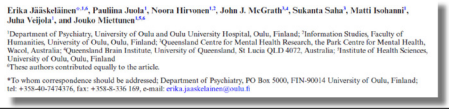
Resources

Heterogeneity of Schizophrenia



Tandon R, et al. *Schizophr Res*. 2009;110(1-3):1-23.

A Systematic Review and Meta-analysis of Recovery in Schizophrenia


Erika Jääskeläinen[1,2,6], Pauliina Juola[1], Noora Hirvonen[1,2], John J. McGrath[3,4], Sukanta Saha[3], Matti Isohanni[2], Juha Veijola[1], and Jouko Miettunen[1,5,6]

[1]Department of Psychiatry, University of Oulu and Oulu University Hospital, Oulu, Finland; [2]Information Studies, Faculty of Humanities, University of Oulu, Oulu, Finland; [3]Queensland Centre for Mental Health Research, the Park Centre for Mental Health, Wacol, Australia; [4]Queensland Brain Institute, University of Queensland, St Lucia QLD 4072, Australia; [5]Institute of Health Sciences, University of Oulu, Oulu, Finland
[6]These authors contributed equally to the article.

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Conclusions:
Based on the best available data, approximately, 1 in 7 individuals with schizophrenia met criteria for recovery. Despite major changes in treatment options in recent decades, the proportion of recovered cases has not increased.

Jääskeläinen E, et al. *Schizophr Bull.* 2013;39(6):1296–1306.

Specified Aims of Recovery After an Initial Schizophrenia Episode (RA1SE) Initiative

- Develop a comprehensive and integrated intervention to
  - Promote symptomatic recovery
  - Minimize disability
  - Maximize social, academic, and vocational functioning
  - Be capable of being delivered in real-world settings utilizing current funding mechanisms
- Assess the overall clinical impact and cost-effectiveness of the intervention as compared to currently prevailing treatment approaches
  - Conduct the comparison in non-academic, real-world community treatment settings in the United States

Kane JM, et al. *Am J Psychiatry*. 2016;173(4):362-372.

Impact of Untreated Psychosis on Patient Outcomes

DUP and QLS and PANSS Outcomes

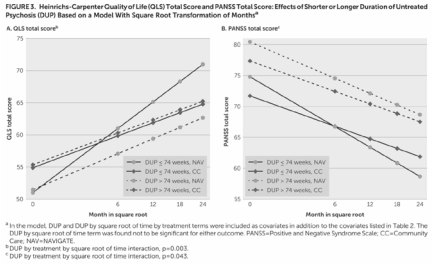


FIGURE 3. Heinrichs-Carpenter Quality of Life (QLS) Total Score and PANSS Total Score: Effects of Shorter or Longer Duration of Untreated Psychosis (DUP) Based on a Model With Square Root Transformation of Months[a]

A. QLS total score[b]

B. PANSS total score[c]

[a] In the model, DUP and DUP by square root of time by treatment terms were included as covariates in addition to the covariates listed in Table 2. The DUP by square root of time term was found not to be significant for either outcome. PANSS=Positive and Negative Syndrome Scale; CC=Community Care; NAV=NAVIGATE.
[b] DUP by treatment by square root of time interaction, p=0.003.
[c] DUP by treatment by square root of time interaction, p=0.043.

DUP = duration of untreated psychosis; QLS = quality of life scale; PANSS = positive and negative syndrome scale.
Kane JM, et al. *Am J Psychiatry*. 2016;173(4):362-372.

Challenges in Predicting Treatment Response

- Characterizing drug response
  - Assessing treatment efficacy
  - Nonadherence
  - Treatment duration
  - Polypharmacy (medical and psychiatric comorbidities)
- Patient characteristics
  - Course of illness
  - Comorbidities
  - Unclear diagnostic boundaries
  - Risk of side effects

Antipsychotic Response

- About 70-80% of patients with First-episode psychosis experience a remission in psychotic symptoms within the first year of treatment
- One-year recurrence (weighted mean) 77% following discontinuation of antipsychotic medication
- Two-year - 90%
- Approximately, a third of patients with schizophrenia show limited if any response to first-line antipsychotic medications

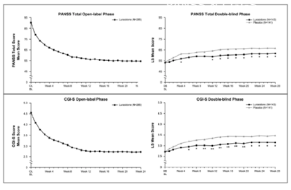
Lieberman JA, et al. *Arch Gen Psychiatry*.1993;50(5):369-376.
Zipursky RB, et al. *Schizophr Res*. 2014;152(2-3):408-414.
Lindenmayer JP. *Psychiatr Q*. 2000;71(4):373-384.

Lurasidone: Long-term Maintenance in Schizophrenia

- Double-blind, placebo-controlled, randomized withdrawal study enrolled adults (N = 676) aged 18 to 75 years with diagnosis of schizophrenia currently experiencing an acute exacerbation
  - PANSS total score ≥ 80 and at least 1 positive subscale item score ≥4
  - CGI-S scale score ≥ 4
- Patients received 12–24 weeks of open-label treatment with lurasidone (40–80 mg/d, flexibly dosed).
- Those reaching stabilization criteria were randomized to lurasidone (N = 144) or placebo (N = 141).

Tandon R, et al. *J Psychopharmacol*. 2016;30(1):69-77.

Lurasidone: Long-term Maintenance in Schizophrenia (cont.)



- The efficacy of lurasidone for the maintenance treatment of patients with schizophrenia was demonstrated
- In the double-blind phase, lurasidone significantly delayed time to relapse compared with placebo reflecting a 33.7% reduction in risk of relapse
- Probability of relapse at the double-blind week 28 endpoint was 42.2% in the lurasidone group and 51.2% in the placebo group.
- Minimal changes in weight, lipid, glucose, and prolactin were observed throughout the study.

Tandon R, et al. *J Psychopharmacol*. 2016;30(1):69-77.

Brexpiprazole: Long-term Maintenance in Schizophrenia

- FDA has approved labeling update for maintenance treatment of schizophrenia (September 24, 2016)
  - Adults (N = 202) with schizophrenia aged 18 to 65 years in a long-term randomized withdrawal trial
  - Cross-titration from a prior antipsychotic to brexpiprazole and a 12 to 36-week, single-blind brexpiprazole stabilization phase.
  - After symptomatically stable on brexpiprazole for 12 consecutive weeks in the stabilization phase, patients randomized in a double-blind treatment phase to either brexpiprazole (N = 97) or placebo (N = 105).

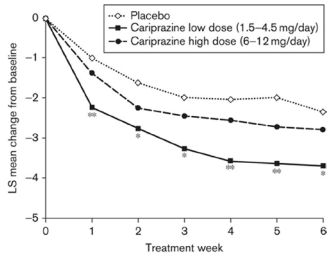
Fleischhacker WW, et al. *Int J Neuropsychopharmacol*. 2016 Oct 13. pii: pyw076.

Brexpiprazole: Long-term Maintenance in Schizophrenia (cont.)

- The primary efficacy endpoint was the time from randomization to impending relapse. Safety and tolerability were also assessed.
- Relapse determined by worsening symptoms defined by changes in PANSS or CGI-I scores; hospitalization for worsening psychotic symptoms; suicidal behavior or; violent/aggressive behavior.
- The final analysis demonstrated a statistically significant longer time to relapse (13.5% brexpiprazole vs 38.5% placebo) (hazard ratio: 0.292, $p < .0001$) in patients randomized to brexpiprazole (1 mg/day to 4 mg/day) compared to placebo.

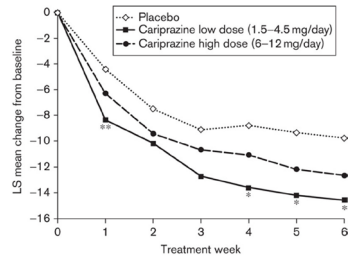
Fleischhacker WW, et al. *Int J Neuropsychopharmacol*. 2016 Oct 13. pii: pyw076.

Low-Dose Cariprazine Significantly Reduces PANSS Negative Scores



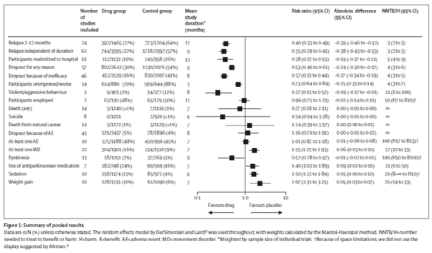
Durgam S, et al. *Int Clin Psychopharmacol*. 2016;31(2):61–68.

Low-Dose Cariprazine Significantly Reduces PANSS Total Scores



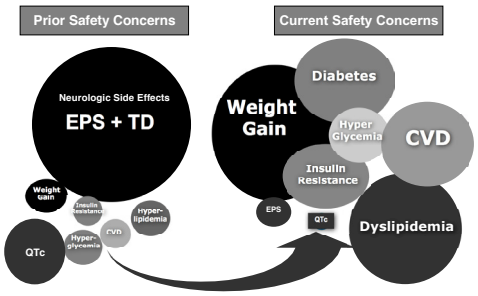
Durgam S, et al. *Int Clin Psychopharmacol*. 2016;31(2):61–68.

Antipsychotics vs. Placebo for Relapse Prevention in Schizophrenia



Leucht S, et al. *Lancet*. 2012;379(9831):2063-2071.

Side Effects of Atypical Antipsychotics: Shift in Risk Perception



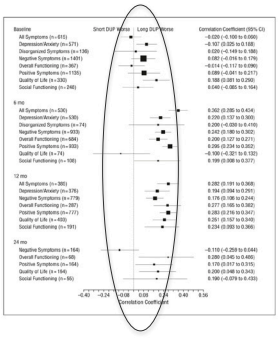
Metabolic Adverse Effects of FDA-Approved Antipsychotic Agents

Antipsychotic	Weight Gain	Diabetes Risk	Dys-lipidemia
Aripiprazole*	Low	Low	Low
Asenapine	Low to moderate	Low	Low
Brexpiprazole	Moderate	Low to moderate	Low to moderate
Cariprazine	Low	Low	Low
Clozapine	High	High	High
Iloperidone	Moderate	Low	Low

Antipsychotic	Weight Gain	Diabetes Risk	Dys-lipidemia
Lurasidone	Low	Low	Low
Olanzapine*	High	High	High
Paliperidone*	Low to Moderate	Low	Low
Quetiapine*	Moderate	Moderate	Moderate
Risperidone*	Moderate	Moderate	Low
Ziprasidone*	Low	Low	Low

*Includes all formulations
[Package Insert]. Drugs@FDA Website.

Association Between Duration of Untreated Psychosis and Outcome



Marshall M, et al. *Arch Gen Psychiatry.* 2005;62(9):975-983.

Lurasidone: Long-term Maintenance in Schizophrenia

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Tandon R, et al. *J Psychopharmacol.* 2016;30(1):69-77.

Optimized Intervention and Team

- Multi-element (e.g., psychiatric care and medications, supported education/ employment, skills and substance abuse treatment, family support, suicide prevention)
- Multi-disciplinary team
  - Team Leader (Master's-level clinician)
  - Supported employment/supported education specialist
  - Recovery Coach (self-management, substance abuse, family)
  - Psychiatrist
- Individualized approach
- Developmentally flexible

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WC-034-071117-03
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