

EXPERT CONSULTANTS

John M. Kane, MD (Co-Chair)
Professor, Psychiatry, Neurology,
and Neuroscience
Albert Einstein College of Medicine
Chairman, Department of Psychiatry
The Zucker Hillside Hospital
Glen Oaks, New York

Douglas L. Noordsy, MD (Co-Chair)
Associate Professor of Psychiatry
Dartmouth Medical School
Lebanon, New Hampshire

**Lawrence J. Cohen, PharmD, BCPP,
FASHP, FCCP**
Professor of Pharmacotherapy
Washington State University College
of Pharmacy
Assistant Director for
Psychopharmacology Research
and Training
Washington Institute for Mental Illness
Research and Training
Spokane, Washington

**Robert L. Dufresne, PhD, PhD,
BCPS, BCPP**
Professor of Pharmacy
University of Rhode Island College
of Pharmacy
Kingston, Rhode Island
Psychiatric Pharmacotherapy Specialist
Providence VA Medical Center
Providence, Rhode Island

Joseph Parks, MD
Chief Clinical Officer and
Division Director
Comprehensive Psychiatric Services
Missouri Department of Mental Health
Jefferson, Missouri

Stephen Saklad, PharmD, BCPP
Director, Psychiatric Pharmacy
Program Pharmacotherapy Education
and Research Center
University of Texas Health
Science Center at San Antonio
San Antonio, Texas

PUBLISHING STAFF

Director of Scientific Content
Jeff Prescott, PharmD, RPh
Contributing Editor
Amy Lodolce, PharmD, BCPS
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Carolyn S. Rohrs, PharmD
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Designer
Ray Pelesko

A Supplement to

THE AMERICAN JOURNAL OF
MANAGED CARE

THE APPLICATION OF EVIDENCE- BASED MEDICINE IN EVALUATING FORMULARY OPTIONS: PAYER PERSPECTIVES

This supplement to *The American Journal of Managed Care* is based on presentations and discussions from a roundtable meeting comprising expert consultants. This meeting was sponsored by Eli Lilly and Company, held in Detroit, Michigan, on July 18, 2008. Part 1, published in December 2008, covered the *Importance of Early and Effective Pharmacologic Treatment in Schizophrenia*. The second installment in the series, *Evaluating Evidence-Based Medicine: Clinician and Payer Perspectives and Applications for Schizophrenia*, was published in February 2009. (All 3 parts of the series can be viewed online at www.ajmc.com.)

ROLES AND RESPONSIBILITIES OF THE CONTEMPORARY P&T COMMITTEE AND FORMULARY

Traditionally, Pharmacy and Therapeutics (P&T) committees within hospitals, clinics, and health systems maintained formularies for basic inventory management and general oversight of the medication use process. Over time, cost-control measures were introduced, mainly in the form of restrictions for certain drugs.^{1,2} Today, formulary management systems, administered by P&T committees in both institutions and managed care organizations, encompass a range of activities that focus on safe and cost-effective medication use management.¹ In addition to formulary management, the P&T committee typically has oversight of all medication policies and procedures, drug use evaluation, adverse drug event monitoring and reporting, and some aspects of medical staff education. Most recent responsibilities include promotion of rationale and safe medication therapy, in turn improving quality of care, safety, and clinical outcomes.^{1,2} Cost management continues to be a focus of P&T committee activity; however, the focus has moved from use of pure formulary restriction to evidence-based pharmacoeconomic evaluations and development of usage guidelines, prior authorization procedures, and therapeutic interchange policies.¹ Formulary decision making will always be heavily influenced by pharmacoeconomic issues, although patient safety and effectiveness outcomes are now more central to the decision-making process.¹

Current challenges faced by P&T committees

The traditional P&T committee role of formulary management and decision making is much more complex in today's healthcare environment.¹ Evaluation of drugs for inclusion on the formulary now integrate efficacy, safety, and pharmacoeconomic considerations from unbiased evidence-based evaluations to support improved patient outcomes across the continuum of care,¹ while several other factors confound the decision-making process of every P&T committee.

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Professor of Pharmacy
University of Rhode Island College
of Pharmacy
Kingston, Rhode Island
Psychiatric Pharmacotherapy Specialist
Providence VA Medical Center
Providence, Rhode Island

Joseph Parks, MD
Chief Clinical Officer and
Division Director
Comprehensive Psychiatric Services
Missouri Department of Mental Health
Jefferson, Missouri

Stephen Saklad, PharmD, BCPP
Director, Psychiatric Pharmacy
Program Pharmacotherapy Education
and Research Center
University of Texas Health
Science Center at San Antonio
San Antonio, Texas

PUBLISHING STAFF

Director of Scientific Content
Jeff Prescott, PharmD, RPh
Contributing Editor
Amy Lodolce, PharmD, BCPS
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Carolyn S. Rohrs, PharmD
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Current challenges faced by P&T committees

The traditional P&T committee role of formulary management and decision making is much more complex in today's healthcare environment.¹ Evaluation of drugs for inclusion on the formulary now integrate efficacy, safety, and pharmacoeconomic considerations from unbiased evidence-based evaluations to support improved patient outcomes across the continuum of care,¹ while several other factors confound the decision-making process of every P&T committee.

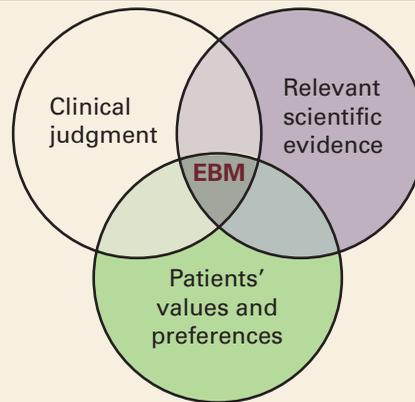


New, costly agents. The cost of healthcare continues to increase in all areas; however, the percentage of healthcare dollars spent on prescription drugs has risen sharply.³ In 2006, \$216.7 billion was spent on prescriptions in the United States, more than 5 times higher than in 1990.⁴ Spending for prescriptions is projected to continue to rise with expanded usage under Medicare Part D, new indications for existing drugs and use of specialty drugs, in addition to the leveling off of use of generics and continued flow of new drugs on the market.⁴

Regardless of potential benefits of a new agent, the cost must be weighed with the magnitude of the benefits. The pressure on P&T committees to control expenditures can be tremendous.⁵ There are several options for approaching these challenging cost issues with effective formulary management. For formulary decision making, an unbiased, evidence-based review of the literature for efficacy is paramount, while the use of internal prescribing, outcomes data, and benchmarking programs can assist in determining the appropriateness and need for a given patient population.¹ Cost-benefit modeling can be used, particularly for integration into clinical usage guidelines. Consideration of all associated costs, not only the cost of the drug, should be included in pharmacoeconomic evaluations.¹ Tiered formularies, in addition to or in coordination with stepwise usage guidelines, help stem the cost of prescription expenditures.^{6,7} Development and use of drug management policies are crucial elements of formulary management, not only for cost, but also for patient safety. Clinical practice guidelines and other utilization policies can increase use of generics, maximize therapeutic interchange, limit use of certain drugs to specialty providers, and decrease variability in practice.¹ Although a challenge to implement, clinical practice guidelines improve patient outcomes and decrease cost.¹

Figure

What Is Evidence-Based Medicine (EBM)?⁸⁻¹⁰



Adapted from Sackett DL, et al. *BMJ*. 1996;312(7023):71-72; Muir Gray JA. *Evidence-Based Healthcare*. 1997.

The role of EBM in policy development. As discussed previously in this series, evidence-based medicine (EBM) is an integrated approach to the decision-making process, using individual clinical expertise in combination with the best research evidence and patient preferences (Figure).⁸⁻¹⁰

The focus of EBM is to integrate the results of well-designed clinical effectiveness trials with other key aspects of good clinical care.

The goal is to maximize the effectiveness of care in order to improve the quality and quantity of life for patients.⁸

The focus of EBM is to integrate the results of well-designed clinical effectiveness trials with other key aspects of good clinical care. Some clinicians misunderstand the concept of EBM as an approach that relies solely on clinical trial results, to the exclusion of clinical experi-

ence and judgment. As opposed to pure research or cost-efficacy-driven guidelines, EBM practice incorporates patient preference and clinical experience as key features. While EBM evaluates therapy effectiveness (or “will it work”), efficacy is a determination of usefulness (or “can it work”) in the controlled setting of a clinical trial. Effectiveness is a measure of efficacy when applied to everyday patient care, given the confounding variables present in the real world.^{10,11} EBM evaluation thus takes the question to the next step, critically evaluating the applicability of a therapy to patient care.

Given the difficult decisions facing today’s providers and payers, EBM is more of an opportunity than a challenge. EBM principles are the basis upon which expert practice guidelines are written. P&T committees can use the same approach to integrate EBM into formulary management efforts, using clinical guidelines to influence prescriber practices to maximize patient safety and cost outcomes. Currently, there is a call for “best practices” (ie, evidence-based guidelines) for the treatment of schizophrenia to avoid trial-and-error prescribing, which can lead to suboptimal patient outcomes and



increased cost. P&T committees can lead the way with use of EBM for best practice development and bring together—in the best interest of the patient—providers and payers for optimization of cost-effective care.

The silo-mentality approach to health system/payer management.

One challenge not often mentioned in formulary management and cost control is of the silo-mentality approach to health system/payer management. Traditionally a business-world term, a *silo* is an independent operating sector that may not effectively communicate or work with the other sectors. Silos are unavoidable in large business sectors, although businesses recognize the need to organize silos according to customer needs.¹² Organizations with a customer focus strive to transcend silos with coordination, cooperation, capability development, and connection.¹²

In healthcare, silos have been described in coordination of inpatient and outpatient care,^{13,14} as well as for a variety of specialty care areas, including mental healthcare.^{15,16} As patients or providers attempt to navigate the healthcare system, the lack of integration between the sectors, such as primary to specialty care, presents barriers. For example, an internist refers a patient to a psychiatric clinic for treatment of schizophrenia, yet the patient is told there is an 8-week wait for a new patient appointment, therefore becoming at high risk for being lost to follow-up. The outcome of silos in healthcare is reduced access to care.^{15,17}

The silo thought process may be especially problematic with regard to pharmacy benefits, as pharmacy benefits are commonly contracted from a separate entity apart from the medical plan benefit.¹⁷ As a result, budgets are separate; therefore, the silo mentality fails to promote integration of care and can lead to cost shifting, as each benefit plan looks to minimize their cost for the care

of each patient. Use of such carve-out specialty coverage controls cost through prior authorization and utilization limits,¹⁷ yet involves another budget and presents one more system for a patient to navigate. Lack of medical and pharmacy benefit coordination discourages preventive care and relegates decision making to the patient (the consumer).^{17,18} For example, a pharmacy benefit plan may cover only drugs used to control diabetes, but not preventive therapies such as cardioprotective agents that prevent the progression of disease, leaving the medical benefit plan to cover the treatment of complications and the patient with suboptimal outcomes.¹⁸ Following the business model, healthcare payers should be a customer-focused industry and work to transcend silos and organize according to patients' needs.

administratively convenient for payers. It is imperative to model healthcare outcomes across the spectrum versus drug cost alone, to recognize the cost savings of providing preventive care versus the cost of untreated illness, and to integrate an extended perspective on cost savings, in order to not only view current expenditures, but also the impact on long-term and lifelong economics.

There are a number of treatment barriers specific to patients with schizophrenia seeking healthcare; therefore, care as usual may not meet their needs.^{15,19} Because of the high rate of unemployment, many patients are uninsured, limiting their access to providers. Internists not trained to work with psychiatric patients may dismiss patients' somatic complaints as a component of their mental illness, hindering treatment.¹⁵ Patients

It is imperative to model healthcare outcomes across the spectrum versus drug cost alone.

It's not surprising that healthcare payer systems are fragmented, as healthcare itself remains very fragmented, often with little collaborative management. Medicine, psychiatry, and pharmacy all remain silos, with independent management and budgets; yet all are expected to work together for seamless patient care. For payers, each benefit plan is challenged to reduce costs, yet they lack access to integrated data that would permit evaluation of the "big picture," as well as whether there is any incentive to manage the whole patient. This often results in different services working at cross-purposes to each other. For example, the cost of a highly effective drug may severely limit its use although the cost of increased relapse and hospitalization may be a multiple of that drug's annual cost. Although the silo approach often fails to improve outcomes and reduce costs, it persists in part because it is

with severe mental illness, such as schizophrenia, have a high number of chronic medical conditions, yet the lack of treatment integration between the mental health and general health sectors limits access to adequate primary care for many patients.¹⁵ In addition, patient perception of barriers may be augmented by distrust of providers.

A decision to stop drug treatment may be made unilaterally by the patient, by the physician, or by both together. Reasons for medication discontinuation include the following^{20,21}:

- Drug-related reasons (eg, lack of efficacy; adverse effects)—ie, reasons related to drug effectiveness.
- Patient-related reasons (eg, lack of insight regarding the illness; misconceptions about the need for continued treatment; cultural beliefs; cognitive impairment).



- Environmental influences (eg, breakdown of the therapeutic alliance; lack of family support; cost).

Patient perception is a critical factor in antipsychotic adherence. Perceived risk and benefit of both the illness and the treatment are key components in the steps toward recovery and strong predictors of medication duration, symptom improvement, and quality of life.^{19,22} In addition, family and peer training can augment patient trust of the system and overall positive outcomes.¹⁹

that have predictable and substantial differences and minimal side effects. Ultimately, all antipsychotics need to be available, with none completely off formulary.²³

If any prior authorization is required, it should be flexible, rapid, and responsive. Ease of access can bolster patient confidence, which makes selling a patient on the idea of trying a new therapy less cumbersome. For example, a lengthy approval process for a depot drug in a nonadherent patient could be seen as “I’m a bad patient, I didn’t take my medicine, and now I have to

cal rating scales are available and should be used for consistent outcomes measurement.

Perhaps most important, patients need and value open access to care. Faster access to care means a shorter time to remission. Coordination of care—primary care to psychiatry—as well as rapid referral to psychiatry will ease patient transition to specialty care and maintain patient confidence in the care plan.¹⁵ New patient appointments with psychiatry need to be available without lengthy waits. Multiple antipsychotic treatment options should be available to allow clinicians to optimally match the treatment to patient needs. As previously mentioned, if there is any prior authorization, it should be flexible, rapid, and responsive, without delay of therapy initiation.²³ Finally, use of early case management is vital to support patients at highest risk of being lost in the system.

Patients need and value open access to care. Faster access to care means a shorter time to remission.

Finally, overall patient satisfaction needs to be maximized when initiating antipsychotic therapy. As with any medical treatment, the incentive to continue treatment is greater if the benefit is seen sooner.

Opportunities to reduce or prevent barriers. With each challenge comes an opportunity for improvement. There is little that healthcare administrators can do to reduce the patient and family barriers in the care of a patient with schizophrenia; however, we need to eliminate as many barriers as possible to significantly reduce system and payer barriers. The goal should be the development of systems for keeping patients in care and medicated as much as possible to improve long-term outcomes. Convenience can improve adherence; therefore, ease in obtaining medication therapy is important for maximizing positive patient perception. Many would argue this should include access to all available antipsychotic drugs. At a minimum there needs to be immediate first-line access to antipsychotic drugs

get a shot.” It’s seen as punishment and not as a convenience. If patient perception is the key to medication adherence and successful outcomes, all aspects of the system should work together to convey a positive, customer-focused attitude toward each patient. Escalating cost of drug therapies demands more effective utilization, through education and evaluation of outcomes. This is particularly crucial with early and effective treatment. Additional resources are needed to educate patients and their families, and to motivate them for what is a very challenging battle. First-episode patients and their support systems need help to get on board with the idea that schizophrenia is a significant illness that needs aggressive treatment, which requires significant time with each first-episode patient—time that may not be reimbursed. Reimbursement based on time and resources spent using approved scales of measurement can allow time allocation for appropriate care. Relative to general medicine, there are fewer objective measures in clinical psychiatry; however, numeri-

P&T challenges specific to mental health. Treatment of patients with schizophrenia is a challenge, starting with the nature of the disease. Patients can be divided into early responders and nonresponders, which predict long-term response to medication. Despite equivalent aggressive therapy, up to 20% of patients may not respond. Even among responders, relapse and recurrence are common. Other challenges include high patient unemployment rate and subsequent lack of funding for care (no insurance) and expensive drug therapies. The total (direct and indirect) excess cost of schizophrenia in the United States in 2002 was estimated to be approximately \$62.7 billion. Of that amount, direct healthcare costs accounted for \$22.8 billion—including approximately \$8.0 billion for long-term care, \$7.0 billion for outpatient care and professional fees, \$5.0 billion for prescription drugs, and \$2.8 billion for inpatient care.²⁴ Response to therapy is highly variable among patients,



which can lead to patient frustration, distrust, and treatment non-adherence. Co-occurring disorders such as substance abuse are common and contribute to treatment

nonresponse and nonadherence. All of these factors need to be considered regarding formulary guidelines for the treatment of patients with schizophrenia.^{19,21,25,26}

Consideration for early, aggressive treatment. The goal of early, aggressive treatment is to reduce the overall burden of the disease to each affected individual and to society.

Table.

Basing Treatment Decisions on Systematic Measures of Antipsychotic Response³⁵

The Initial Drug Trial

1. **Have a treatment plan.** Set response expectations for each patient. Quantify target signs and symptoms at baseline and evaluate over time.
2. **During the trial of the first drug, measure response** early and over time using rating scales, and predict **future response** if possible. Optimum doses vary among patients and stages of schizophrenia; later episodes may require higher doses than the first episode.
3. **To measure response, use validated assessment tools** such as the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS). If the patient does not respond after a short trial (eg, 2 weeks), treatment change may be necessary.

Other Considerations in Treatment Change Decisions

1. **If response is inadequate, reconsider the diagnosis.** Consider a comorbid condition affecting treatment response (eg, substance abuse, hypothyroidism, or urinary tract infection in the elderly patient).
2. **Ensure that the patient is adhering to treatment.** Use direct observed therapy, alternate dosage forms (liquids, rapid dissolving, or long-acting intramuscular). Monitor with blood levels, particularly in nonresponders, to ensure a therapeutic concentration.
3. **Execute only 1 change at a time** in the treatment plan.
4. **Consider whether dosing is optimal.** Dose increases should be done cautiously, with the use of rating scales.
5. **Psychosocial interventions may add some benefit.**
6. **Irrational prescribing of adjunctive drugs** (mood stabilizers, anticonvulsants, and additional antipsychotics) **complicates response assessment and adverse event risk.** We cannot accurately predict who will respond early. Sometimes another week of monotherapy may prove the original drug to be effective. Although use of polypharmacy is common, evidence that adding another atypical antipsychotic will yield a more robust response is inconsistent at best. Polypharmacy will not always alleviate adverse effects of an antipsychotic. If adverse effects occur, first consider dose reduction. Polypharmacy may have inadequate justification and unpredictable results. Monotherapy is easier to monitor, interpret, and document; easier for patients; and may be more effective.
7. **Switching atypical antipsychotic agents may benefit patients who do not respond to an initial antipsychotic.** The process for switching varies; however, a period of overlap may be recommended to maintain therapeutic levels and avoid withdrawal effects.
8. **Switching carries some risk,** because the new drug's effectiveness for this patient is unknown, and its adverse effects may be different. Switching is common due to patient dissatisfaction with their current medication.
9. **We do not yet have conclusive data to recommend particular drugs to increase response under particular clinical circumstances.** Data that suggest preference for one antipsychotic over another are based on longer trials beyond the scope of this article. When switching, it is best to weigh the potential for better efficacy against the risk of adverse effects. Family history may identify patients at risk for many conditions. Genetic testing may be available in the near future. Effective safety monitoring begins with charting good baseline data in potential problem areas.



Early and effective pharmacologic intervention for all patients with new or recurrent psychotic symptoms may improve both short- and long-term outcomes.²⁷ In acute-phase schizophrenia—whether first episode or relapse—prompt antipsychotic treatment is recommended to reduce emotional distress, minimize disruption to the patient’s life, and reduce the risk of dangerous behaviors.²¹

and disability, evaluation of cost-effectiveness with psychiatric drugs is imperative.^{29,30} While it is not currently possible to predict which individual patient will do best on which individual antipsychotic in patients who have not previously taken antipsychotics, it is well-established that administratively forcing a patient to switch off an antipsychotic medication that they are stable on usually

maintain emergency access to drugs during the appeals process.³⁰

With respect to the treatment of schizophrenia, use of formulary restriction policies has been associated with higher rates of medication discontinuation and of hospitalization, with only a minimal decrease in pharmacy costs despite decreased nonpreferred drug use.³² Another cohort analysis found a similar shift toward preferred formulary agents, with minimal cost benefit.³³ A closed formulary or cumbersome prior authorization process discourages aggressive therapy escalation or treatment of resistant patients and sends the message to the patient that they are difficult to treat. In addition, lengthy prior authorization procedures can delay initiation of therapy.³⁴

Therefore, many providers argue for availability of all antipsychotics, particularly given patient variability in response (Table).^{35,36} Some suggest that wider availability of agents, both traditional and atypical antipsychotics, could decrease expenditures,³⁷ by increasing the chance of using the best drug for each individual patient. Concerns regarding restriction were prominent in the development of Medicare Part D, wherein the Centers for Medicare & Medicaid Services guidelines require Medicare plans to cover “all or substantially all” antidepressants and antipsychotics.³⁸ Whenever possible, patients should be treated based on clinical and medical history.³⁹ If a person is shown to do well on a particular drug, then that drug should always be immediately available. Access to an open formulary allows patient and provider coordinated decision making and an increased chance of positive “perceived medication benefit” and medication adherence. As part of routine medication management, P&T committees should utilize provider education, to prevent inappropriate use of antipsychotics and to change prescribing practices, rather than restrictive policies.^{34,39}

With respect to the treatment of schizophrenia, use of formulary restriction policies has been associated with higher rates of medication discontinuation and of hospitalization, with only a minimal decrease in pharmacy costs.

Continuous maintenance appears to prevent relapse more effectively than intermittent treatment strategies, in which antipsychotics are discontinued after remission and restarted when symptoms of impending relapse occur.^{21,27,28} Formularies should reflect these findings and support clinical practice guidelines for use of early, aggressive therapy in all patients with schizophrenia.

Options for nonresponders. Given the complexity of this illness, formularies need to consider options for patients with schizophrenia, and not just the portion that are early responders with sustained relapse-free recovery. Formulary considerations for psychiatric drugs are similar to those in other areas of medicine; however, significant interpatient variability and high nonresponse rates confound the restriction of therapies. Up to 20% of patients with schizophrenia and one third with depression do not respond to first-line therapy.²⁹ Because nonresponse can lead to an increase in healthcare utilization (clinic visits, hospitalization, other nondrug costs)

results in poorer outcomes. “Fail-first” formularies that require failure of a preferred agent for authorization of second-line therapies often focus on acquisition cost for determination of the first-line agent. However, not all organizations base decisions on acquisition cost alone and often find it more valuable to look at costs beyond acquisition price of drugs for the treatment of schizophrenia.

Less is known about the effect of formulary cost-control policies in psychiatry than general medical conditions.³¹ Therapeutic substitution and preferred medication policies assume high substitutability among the drugs in a class; however, this may not be the case with heterogeneous psychiatric patients.³¹ The cost savings in drugs may result in escalation of costs in other healthcare expenditures.³⁰ Ethical issues must be considered in formulary restriction. Based on the code of psychiatric ethics, the New Jersey Psychiatric Association recommended that formularies use evidence and consensus with psychotropic formulary decisions, maintain the rights of patients for their preference, avoid use of mandatory “step therapy,” and



In reality, the great divide in the cost of treating patients with schizophrenia is between the responders and nonresponders as well as the adherent and nonadherent. Despite the similarity in medication cost, the total healthcare cost of treating the robust responders is about half the cost of treating the early nonresponders.²² We may not be able to predict which patient will be a robust responder versus a nonresponder, or from which particular antipsychotic drug they will get the best therapeutic response. However, in the end, similar to treatment of cancer, change seems inevitable, and the drug you start with isn't always the drug you end with. A diverse antipsychotic formulary allows care providers to direct therapy to each specific patient.^{36,40} Clearly, a formulary must be main-

tained for containment of escalating medication costs. Open formularies allow for provider autonomy, but they do not align with clinical guidelines for assurance of safe and efficacious treatment. Restricted formularies have proven pharmacy cost savings, but these savings are not necessarily quantified across the care system. Cost of drugs alone cannot quantify quality of care.^{32,33,41}

CONCLUSION

Treatment of patients with schizophrenia presents many challenges, by nature of the disease, patient barriers, and silos of care. Use of early, aggressive treatment, in combination with personalized treatment matching, a well-structured support system, and a coordinated care plan, gives the best chance for recovery.

P&T committees are challenged with containing expenditures, yet maximizing patient outcomes and safety. Standard formulary management cost controls are a paradox when used with schizophrenia. Although intended to streamline care and decrease costs, restrictive policies may not meet the needs of patients with schizophrenia, and data to date do not support their association with positive patient outcomes. Implementation of EBM is best suited to meet the needs of patients, and can play a significant role in overall healthcare expenditures. EBM can help bridge the gap between open and restrictive systems, with integration of effectiveness, tolerability, patient preference, and provider experience, to optimize patient outcomes.

DISCLOSURES

The faculty report the following disclosures:

LAWRENCE J. COHEN, PHARM D, BCPP, FASHP, FCCP:
CONSULTANT/ADVISORY BOARD: ASTRAZENECA, LILLY, WYETH;
HONORARIA: ASTRAZENECA, FOREST, LILLY.

ROBERT L. DUFRESNE, PH D, PH D, BCPS, BCCP:
ADVISORY BOARD: JOHNSON & JOHNSON, ELI LILLY; EXPERT TESTIMONY: ASTRAZENECA; LECTURER: JOHNSON & JOHNSON, ELI LILLY.

JOHN M. KANE, MD:
CONSULTANT/ADVISORY BOARD: BRISTOL-MYERS SQUIBB, JANSSEN, LILLY, OTSUKA, PGxHEALTH, WYETH; LECTURER: BRISTOL-MYERS SQUIBB, JANSSEN, LILLY, OTSUKA;
STOCKHOLDER: MEDAVANTE.

DOUGLAS L. NOORDSY, MD:
CONSULTANT/ADVISORY BOARD: LILLY;
GRANTS: JANSSEN; HONORARIA: ASTRAZENECA, LILLY, PFIZER.

JOSEPH PARKS, MD:
CONSULTANT: ELI LILLY, JANSSEN,

SOLVAY, WYETH; EMPLOYEE: MISSOURI DEPARTMENT OF MENTAL HEALTH; PENDING GRANTS: NATIONAL INSTITUTE OF MENTAL HEALTH; GRANTS RECEIVED: SUBSTANCE ABUSE & MENTAL HEALTH SERVICES ADMINISTRATION; HONORARIA: NATIONAL ALLIANCE ON MENTAL ILLNESS ALABAMA.

STEPHEN SAKLAD, PHARM D, BCPP:
ADVISORY BOARD: LILLY ACADEMIC PHARM D ADVISORY BOARD;
HONORARIA: DARTMOUTH UNIVERSITY; SPEAKERS' BUREAU: BRISTOL-MYERS SQUIBB, PFIZER.

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A206



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