REVIEW

Tying comparative effectiveness information to decision-making and the future of comparative effectiveness research designs: the case for antipsychotic drugs

The outcome of comparative effectiveness research on antipsychotic drugs, specifically the National Institute of Mental Health-funded CATIE trial, has raised questions regarding the value of second-generation antipsychotic drugs and has sparked a debate regarding their accessibility through public insurance. We reviewed the evidence on the impact of access restrictions for antipsychotic drugs in Medicaid programs and found that such restrictions resulted in increases in overall costs and a possible decline in the quality of care. We attribute this unwanted outcome to limitations in comparative effectiveness research designs that fail to inform either clinical or policy decision-making. We enumerate these limitations and illustrate the potential for more innovative comparative effectiveness research designs that may be in line with clinical decision-making using an original analysis of the CATIE trial data. The value of genomic information in enabling better trial design is also discussed.

Keywords: antipsychotic drugs ■ heterogeneity ■ Medicaid ■ pharmacogenetics
■ prior authorization ■ schizophrenia

Our primary goal in this paper is to highlight the consequences of information generated from comparative effectiveness research (CER) studies that fail to explore heterogeneity in treatment effects. We present our views in the context of schizophrenia and antipsychotic drugs with the hope that future CER study design will take our recommendations into consideration.

Antipsychotic drugs (APDs) represent a huge expenditure for state Medicaid programs; the primary payer, through public insurance, for low-income patients with schizophrenia bipolar disorder, major depression and organic dementias with psychotic features [101]. The massive expenditure is the result of the high prevalence of these disorders, the need for prolonged treatment in many cases, and the high unit costs of these drugs, despite the fact that some are no longer patent protected. Following the introduction in the 1990s of the atypical APDs (AAPDs), sometimes referred to as second-generation APDs, total expenditures for this drug class accelerated partly because of the preference by clinicians for these drugs, based upon perceived advantages in efficacy for various dimensions of psychopathology, cognition, compliance and side effects [1]. A major safety advantage of the AAPDs is fewer motor side effects [2], including tardive dyskinesia, which has been shown to increase mortality [3]. These advantages, which have been attributed to differences in their pharmacology compared with that of the typical APDs (TAPDs), sometimes referred to as first-generation APDs, are disputed by some [4], especially in light of recent

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CER studies. For example, the US-based CATIE trial has challenged the advantages of the AAPDs over TAPDs and reported a minimal advantage for only one AAPD, olanzapine, and no advantage for quetiapine and risperidone, compared with perphenazine, a TAPD [5]. However, the CATIE data have been subject to rigorous analysis and found to be flawed, without significant value for their main goal of determining which drug might be preferred on the basis of efficacy, safety, tolerability and cost-effectiveness [6,7]. Those recommendations of the CATIE study, which recommend a return to TAPDs as first-line treatment, have had only a small influence on prescribing practice in the USA and elsewhere [8]. The same is true for another effectiveness study carried out in the UK, CULASS, which had numerous design flaws [9]. However, debate regarding the comparative effectiveness of these AAPDs persists [102], due in part to the uncertainty in the various measures of efficacy, side effects and patient acceptance in both CATIE and CULASS [10–15,103].

Policy makers have interpreted the results from CER studies on APDs, including results from CATIE and CULASS, in ways that were not intended, reflecting conflicting views among the investigators in these studies [5,9]. Some CATIE investigators stated that their study was not designed to directly answer policy questions such as access to specific APDs, while others suggested that the CATIE results clearly established the policy conclusion that it is wasteful to use public funds to pay for branded AAPDs [16,17], a perspective that has been adopted by some influential media outlets and some pharmacy benefit managers [1,18,104]. Reports on the cost-effectiveness of APDs combined with the fiscal difficulties within state governments have sparked a new and vigorous debate regarding access to the higher-priced AAPDs [19,104]. Subsequent to the publication of CATIE, various states' public health officials have, in fact, restricted coverage for the AAPDs [20].

One of the shortcomings of CER studies of APDs has been the lack of information regarding the heterogeneity in effectiveness of these agents among patients with schizophrenia, the principal patient group included in CATIE and CULASS. Schizophrenia is itself recognized as a syndrome, not a specific disease [105]. Heterogeneity in response to TAPDs and AAPDs on an individual basis has been recognized even at their introduction for core positive symptoms

such as delusions and hallucinations, and for other dimensions of the syndrome such as negative symptoms, cognition and mood/suicidality [21]. Thus, it is to be expected that individual responses to specific AAPDs differ widely because of pharmacodynamic and pharmacokinetic differences among the drugs and individual differences in the neurobiology of the underlying syndrome, based partly upon pharmacogenetic and epigenetic individual differences [22]. Efforts to identify genetic predictors of response to specific AAPDs are being intensively studied [23,24]. There is no reason to expect any one AAPD would be the optimal choice for all patients with schizophrenia, because of the patient variability [19]. With some exceptions (e.g., clozapine for treatment-resistant patients) there are, as yet, no accepted predictors of which particular drug will produce optimal results for a specific patient. In clinical practice, such ambiguity usually leads to sequential trials with multiple drugs in the search for better outcome [25]. This is a lengthy, inefficient, costly and sometimes dangerous process, for example when serious motor or metabolic side effects develop or when suicidal or violent behaviors emerge [22]. Identifying small differences in the average intention-to-treat effects due to initial APD assignments, which is the approach used in most of the CER studies, cannot provide guidance either on insurance coverage decisions or the sequence of drugs that should be tried for a specific patient [5,9]. By contrast, we argue in this paper that CER has the potential to identify optimal navigation processes for patients and insurers by development of effective, dynamic algorithms that can direct treatment decision-making.

An unfortunate consequence of ignoring heterogeneity in drug effects is that most economic evaluation studies, which tend to mirror the CER designs, fail to address important questions regarding insurance coverage. In a recent paper, Basu *et al.* highlighted the costs of ignoring heterogeneity of response for economic evaluations of APDs [26]. It was found that if Medicaid coverage policy had responded to the CER results of CATIE by providing partial coverage that only reimbursed TAPDs and generic risperidone (an AAPD), the savings would amount to 40% of the US\$2 billion spending on this class of drugs over 1.5 years, compared with the pre-CER policy that covered all APDs. However, taking into account the observed heterogeneity in treatment effects, such a policy would incur a net loss (= savings – costs) valued at approximately

25% of class spending due to failure to switch treatments when indicated and the consequent negative impact on quality of life and medical utilizations. Thus, for one of the largest drug classes in one of the major healthcare subsidy programs, adjusting for patient heterogeneity not only alters the magnitude, it actually reverses the direction of anticipated financial benefits to be obtained from a CER analysis [26].

In practice, even when restrictions on certain AAPDs are weakly implemented, many insurers, including many state Medicaid agencies, have applied a variety of access restrictions such as prior authorizations (PAs) and/or stepped-therapy and tiered-formulary designs, aimed at controlling cost growth and hoping to avoid sacrificing overall (average) patient welfare in the process. Some researchers have specifically cautioned against the use of such restrictions that would only permit generics, as the potential effect of such restrictions on the magnitude of cost savings remains unclear [27].

We begin with a brief review of the different types of access restrictions that have been and are used by Medicaid and the evolution over time of policy responses in the form of restrictions on AAPDs by different Medicaid insurers. Second, we review the research literature that has studied the impact of access restrictions to AAPDs on spending and the subsequent health of the patient population. Third, we highlight the need for new methodological approaches in CER for APDs that can help align information with decision-making at policy and individual-patient levels. Specifically, we discuss the need to individualize treatment choices using CER information and present an original analysis of the CATIE data to highlight the potential of new study designs to achieve such a goal. We also discuss some of the latest developments in using genetic markers to predict APD treatment response.

Evolution of access restrictions enforced by Medicaid programs

Formularies are a pharmacy management tool used by payers to restrict access and contain costs of certain pharmaceuticals. Although formularies may serve an educational purpose for physicians regarding the relative benefits of drugs, most modern formularies are incentive based; they provide patients with financial incentives in the form of reduced costs to them, in order to direct them towards choosing those drugs that

cost the insurer less to purchase. Sometimes, these formularies are based on preferred drug lists that offer manufacturers an exemption from restricted access in exchange for discounts. Several approaches are used to implement a formulary in practice. Tiers of formulary listings define the level of cost sharing allowed by the payer. A drug placed in the higher tier is usually associated with a greater amount of cost sharing by patients. PA requires that specific conditions be met before reimbursement is allowed. Often physicians must submit additional information to obtain PA. A closed formulary will preclude coverage for a particular drug.

Of the 47 Medicaid programs included in a 1998 survey, 46 included the three most widely prescribed AAPDs (risperidone, olanzapine and quetiapine) on their formularies, while one program included olanzapine and quetiapine, but not risperidone [28]. Three Medicaid programs (6%) required a PA step for all AAPDs. Even as late as 2003, 4 years after the reintroduction of clozapine – considered the gold standard among the AAPDs for a certain subgroup of patients – most Medicaid programs had avoided instituting any preferred drug list for APDs [29]. By 2005/2006, however, 22 (44%) out of 50 Medicaid programs examined had instituted some PA requirements for AAPDs [20]. Restrictions included required failure of ‘preferred’ medications, called ‘step-therapy PA policies’, or the presence of certain health conditions that would make unrestricted drug access reasonable. Other restrictions on access to APDs instituted by various Medicaid programs include the mandated use of generics and the use of a preferred drug list.

Besides the USA, several other countries such as Australia, The Netherlands, the UK, New Zealand, Italy and Canada employ drug formularies either at a national or local level.

Impact of cost-control interventions & access restrictions to APDs on the health & economic cost of treating patients with schizophrenia

There are only a few studies that have examined the effect of PA policies on prescription medications to treat psychiatric illness in different states (Table 1). Farley and colleagues studied the effect of the Georgia Medicaid step-therapy PA policy for AAPDs on prescription costs and total health service expenditures for patients with schizophrenia [22]. They compared these effects to contemporaneous trends of outcomes in

Table 1. Evaluation of restriction policies on the use of atypical antipsychotics by US state Medicaid systems.

Study (year)	Restriction, time frame	Control	Policy effect	Ref.
Farley <i>et al.</i> (2008)	Step-therapy PA policy in Georgia Medicaid (USA) from 1 November 1996	Pre- and post-PA trends from Mississippi Medicaid (with no PA policy)	US\$19.62 PMPM decrease in AAPD expenditures but an increase of US\$31.59 PMPM in outpatient expenditures, all effects were statistically significant at the 5% level	[22]
Law <i>et al.</i> (2008)	PA in West Virginia (USA), Spring 2003, versus PA in Texas (USA), Spring 2004	Pre- and post-PA trends from all 38 US states with no PA policies Alternative controls: 27 US states with no PA policies on any drug, neighboring states with no PA policies for AAPDs	Immediate drop in market share for restricted drugs by 3.5% patients ($p = 0.003$) in West Virginia and by 2.6% patients ($p = 0.055$) in Texas, with sustained decrease thereafter in West Virginia. No significant change in cost level or trend in total prescription expenditures in either state	[30]
Soumerai <i>et al.</i> (2008)	Step-therapy PA policy in Maine Medicaid (USA); PA policy implemented July 2003 and suspended March 2004 ^a	New Hampshire as comparator state due to geographic proximity, comparable demographic characteristics to Maine and lack of PA requirements for AAPDs	Postpolicy increase (29%; $p = 0.036$) in risk of treatment discontinuities, and spending, as well as a decreased time to treatment discontinuities Policy attributable risk of AAPD treatment gaps of over 30 and 45 days was 1.55 (95% CI: 0.94–2.56; $p = 0.09$) and 1.94 (95% CI: 1.14–3.29; $p = 0.01$), respectively	[31]
Walthour <i>et al.</i> (2010)	Step-therapy PA policy in Georgia Medicaid (USA); July 2003–April 2006	None	Decline in postpolicy trend for the average number of emergency room visits (absolute difference: -0.042 PMPM; relative difference: -20.92%) and average number of hospital admissions (absolute difference: -0.010 PMPM; relative difference: -22.27%)	[32]

^aDue to numerous case reports of adverse effects associated with the policy.

AAPD: Atypical antipsychotics; PA: Prior authorization; PMPM: Per member per month.

patients with schizophrenia from the Mississippi Medicaid program where no such policy was implemented. They found that compared with the Mississippi program, introduction of the PA policy in Georgia (USA) was associated with a decrease in AAPD expenditures, but this was offset by increases in both TAPD and outpatient expenditures. All these effects were statistically significant.

Law and colleagues used a quarterly state-level drug costs and usage measure to evaluate the impact of PA policies in West Virginia (USA; 2003) and Texas (USA; 2004) [30]. Compared with a control group, the PA policies resulted in an immediate drop in market share for restricted drugs in West Virginia ($p = 0.003$) and in Texas ($p = 0.055$), with a sustained decrease thereafter in West Virginia. However, there was no significant change in total cost level or even trends in total prescription expenditures in either state.

In a similar study, Soumerai and colleagues examined the effect of a policy change in Maine Medicaid in July 2003 that incorporated PA on AAPD drugs for schizophrenia [31]. These authors used Medicaid claims between 2001 and 2004 to compare pre- and post-implementation trends in healthcare utilization and compared them to claims from New Hampshire patients as a control. The change to PA in Maine was associated with a 3% increase in preferred TAPD use and a 5.6% decline in nonpreferred AAPD use. There was an average reduction of US\$18.63 per member per month (PMPM) at 8 months after implementation of the PA policy. However, the PA policy was also associated with a 29% increase in treatment discontinuity. Among 151 observed discontinuities, there were 104 gaps in treatment for durations lasting longer than 30 days. As a result of numerous case reports noting adverse effects associated with the policy, including psychosis, the PA policy was suspended in Maine on March 2004 [31].

In a more recent study, Walthour *et al.* examined the impact of introducing a PA policy on antipsychotics in the Georgia Medicaid program in 2004 [32]. Using a cohort of continuously eligible adult Georgia Medicaid recipients with schizophrenia-related diagnoses and documented use of an AD medication, the authors performed a pre- and post-implementation analysis to study the impact of the PA policy. These researchers found that the policy resulted in a significant decline in both emergency department visits (an absolute difference of -0.042 PMPM;

$p = 0.0019$) and average number of hospital admissions (-0.010 PMPM; $p = 0.011$). However, unlike previous studies, the observed change in the use of APDs over time was not contrasted with any control group that would pick up contemporaneous trends in use that were not attributable to the policy change. Thus, no conclusions can be drawn from this study.

Improving the role of CER in public policy of APD access

■ The current disjoint between research & policy

There is a significant body of clinical and health services research which suggests that AAPDs may increase costs without adding significant health benefits [17,33,34]. However, these views – as well as the validity of the studies they are based upon – are contested [6]. By contrast, there is general agreement that due to the heterogeneity in efficacy and tolerability to AAPDs and TAPDs, access to most, if not all, currently available drugs is needed [16,17]. In agreement with this concept, direct evaluations of some Medicaid restriction policies suggest that such restrictions will often adversely impact the health of patients with schizophrenia and are unlikely to generate any overall cost savings. Perhaps the primary reason for such disparate views is that studies attempting to estimate the effect of AAPDs in comparison to TAPDS using observational data methods have compared patient outcomes among regions with higher use of AAPDs to those with lower use. Such methods, in turn, identify an effect for AAPDs that is relevant only to a limited group of patients with schizophrenia [35,36]. Consequently, these estimated effects have limited applicability to the broader patient population and fail to represent effects that a PA policy would have on overall costs and outcomes. Therefore, understanding the heterogeneity in effects across the population remains key to successful CER and the potential for CER to contribute appropriately to policy-making.

■ Heterogeneity: a crucial part of CER going forward

Due to extensive interindividual differences in pharmacodynamic and pharmacokinetic factors that influence efficacy and tolerability, there is much heterogeneity in the outcome of treatment with APDs [5,22]. Access to the entire class may be required to address individual differences, making it necessary for physicians not only to

be knowledgeable about, but also free to choose what they believe to be the optimal treatment for a given patient. There is strong consensus that treatment-resistant and neuroleptic-intolerant patients with schizophrenia will benefit most from treatment with clozapine. Those who argue that low doses of TAPDs are the equivalent of AAPDs rely mainly on the published results of the CATIE and CUtLASS study data to make policy or clinical decisions [6]. The fact that neither study has had any influence on clinical practice may be interpreted to mean that clinicians reject the conclusions of these studies because they fail to be consistent with their clinical observations [37]. The physician's responsibility for choosing the right drug at the right dose for the correct duration of time [38], maintaining patient adherence, and, in this manner achieving good outcomes, may be in conflict with some government's preferred choice that appears to be based on compromised clinical data [8].

A major concern among schizophrenia treatment providers is providing the appropriate AAPD or TAPD to each patient. Reliance on clinical research, such as CER, in order to obtain key information to help guide such decisions is commonplace. The fundamental challenge that has limited the use, or promoted the misuse, of CER in real-life practice is that traditional research designs – which include randomized clinical trials, cohort studies and retrospective data analysis – have all focused on producing a comparison of average results under alternative treatment initiation, often focused on a selected subgroup of the target population. It is widely recognized that different patients respond differently to the same treatment, a phenomenon known as response heterogeneity. Differences in responses by the same patient under alternative treatments constitute treatment-effect heterogeneity. By focusing on average results, CER has traditionally ignored response and treatment-effect heterogeneity. Subgroup analyses (defined by broad observable criteria such as age, race and gender) remain popular methods to assess heterogeneity in treatment effects. While such approaches provide a better understanding of heterogeneity than global averages, they do not harness the power of treatment-effect heterogeneity in improving the quality of our healthcare system.

It is helpful to understand the mechanics of the CER evaluation process to resolve the question of how to use treatment-effect heterogeneity

to improve individual patient outcomes. These are best represented using the concept of potential outcomes, as defined in the statistics and economics literature [39,40].

Potential outcomes represent all the different possible outcomes for the same individual had that individual received either intervention. Theoretically, if the potential outcome under each intervention for each individual were known in advance, then both the individual allocation of treatments and the social policies on access could be optimized. Therefore, most statistical and econometric methods used in CER aim to characterize the distribution of these potential outcomes. However, the combination of traditional research designs and analytical methods do not allow for consideration of the full joint distribution of potential outcomes and comparative effects of individual patients across alternative treatments. Instead, most of the applied literature in health-outcomes research has characterized the marginal distribution of these potential outcomes, with a focus on measures of central tendency of the distribution such as the mean or median. A mechanism that can generate estimates of treatment effects at the individual level rather than at a group level can have substantial value for decision-making. In fact, the recently completed CATIE trial sponsored by the National Institute of Mental Health, with innovative designs on re-randomization, is generating evidence on such individual-level heterogeneity [41,42].

■ An exploratory analysis of treatment-effect heterogeneity using CATIE data

We now present an example of an original analysis from the individual-level CATIE data to make this point. One of the novel design features of CATIE was that when individual patients discontinued their primary treatment, they were re-randomized and assigned to another drug, thereby making it possible to estimate conditional comparative effectiveness estimates. We expressed these estimates in terms of quality-adjusted life years (QALYs) since many of these drugs influence both the symptoms and the side-effect profile in patients. We used the Positive and Negative Syndrome Scale, which measured severity of psychotic symptoms among patients with schizophrenia, to compute a severity index, and to then assign quality-of-life (QoL) 'weights' to each severity category. Similarly, we assigned QoL weights to each of

three common and serious side-effects: akathisia, akinesia and weight gain. Overall, QoL for a patient at any given time was computed by taking the minimum of the symptom-based QoL scores and side effects-based QoL scores. The key outcome on which comparisons were made was computed as the average monthly change in QALYs. Studying the individual-level joint distribution of effects between risperidone (in Phase I trials) and olanzapine or quetiapine (in Phase II trials) among those who discontinued risperidone in Phase I trials, it was clear that the level of response to risperidone before discontinuation is predictive of whether switching to olanzapine or quetiapine will produce better results. Specifically, if monthly change in QALYs while on risperidone was <0.0025 , individuals would probably benefit more by switching to olanzapine. For the others (i.e., with a monthly change in QALYs ≥ 0.0025 while on risperidone), switching to quetiapine was probably to produce better results. These individual-level predictions were based on the individual patient's response to first-line drugs and therefore can be used to generate preferred (and dynamic) sequences of drug use. Unfortunately, traditional CER, and even CATIE, are not powered or even designed to examine these questions with enough precision to generate valid information for guiding clinical decision-making.

■ Emerging role of pharmacogenomics in individualizing CER for patients with schizophrenia

A potential method with a high likelihood of success for addressing the individualized treatment of the patient with schizophrenia involves pharmacogenomic profiling. There is strong evidence that suggests that genetic variability may play an important role, not only in the development of the disease itself but also in the medication response and toxicity in patients with schizophrenia to antipsychotic therapies [17,33]. Pharmacogenomic profiling is potentially able to identify patients who are more likely to benefit from specific treatments (i.e., with a specific AAPD) based on genetic differences, innate and acquired, and thereby improve treatment outcomes and reduce adverse effects. Several genotypes have recently been identified that appear to be associated with the efficacy or tolerability response of patients with schizophrenia to APDs. One recent study, involving 401 patients treated with AAPDs for schizophrenia (300 males and

101 females) found that variants or subtypes of the α_{1A} adrenergic receptor gene were associated with weight gain (the most common side effect of patients treated with AAPDs) [43]. These variants were identified by single nucleotide polymorphisms that provide tags for specific allelic variants. The precise molecular mechanism underlying this association is currently under investigation.

The value of this approach is emphasized by pharmacogenomic evidence based on CATIE data, and replicated in a randomized clinical trial comparing risperidone and olanzapine on metabolic and efficacy measures [44], which showed that a specific haplotype of the *SULT4A1-1* gene, a risk gene for schizophrenia [45], with a particular phenotype [46] significantly explained individual differences in response to olanzapine, but not risperidone [47]. However, although both the CATIE data and that produced by Meltzer *et al.* identified a specific haplotype associated with a poor response to risperidone and a much better response to olanzapine, replication and extension of these findings to determine the specificity and sensitivity of this biomarker is needed before it can be recommended for anything other than research purposes [48]. If replicated, these results clearly show the possibility that pharmacogenomics can be useful to eliminate poor choices and to recommend treatments more likely to be efficacious and tolerable. In the future, development of novel research designs and methods that incorporate pharmacogenetic analyses as early as stages II and III in drug development, could immensely aid the rapid development of effective and safe treatments for specific populations of patients. The elucidation of the mechanisms underlying these associations will increase our understanding of schizophrenia at the molecular level and can facilitate the development and application of individualized treatments. Ultimately, this approach will provide much-needed guidance for physicians and healthcare providers/managers by facilitating individualized treatment of patients with schizophrenia [24,43,49–51].

Conclusion

Prescriber autonomy is essential in treating patients with schizophrenia and it impacts the effectiveness of treating patients using AAPDs. While prescription use by practicing clinicians sometimes does not adhere to evidence guidelines [52,53], we have highlighted the fact that

evidence produced by, for example, CER studies often may not cater towards decision-making at the clinician level. As CER begins to explore treatment-effect heterogeneity to a much larger extent that now, alternative forms of guidelines may emerge that not only respect prescriber autonomy, but also empowers them towards evidence-based decision-making.

While formulary management interventions are important in controlling costs for most medications, the heterogeneity in individual neurobiology and differences among drugs requires individualized treatment. Those who prescribe medications for patients with schizophrenia have the challenge to develop an efficacious and tolerable treatment plan for each of their patients. The management system that determines and controls access to these treatments should therefore aim to aid prescribers in making individualized, informed decisions rather than mandating solutions based on averages. The available body of evidence does not support the notion that implementing PA requirements for AAPDs results in consistent and meaningful cost savings without adversely impacting patient well-being. More importantly, a new era of CER can try to aid understanding of the heterogeneity in treatment effects across alternative AAPDs and devise suitable ways to translate such information into better decision-making. Doing so can optimize the use of continuously evolving expensive technologies such as the AAPDs, without sacrificing patient welfare or squandering public resources.

Future perspective

CER is meant to generate key information that can guide healthcare demand, either through individual-level decision-making or through policy-level access decisions. Having a clear understanding as to what type of information is needed for different levels of decision is central to realize the value of CER. With the creation of the Patient-Centered Outcomes Institute (DC, USA) and the demands in the Affordable Care Act for information that can serve more nuanced subsets of patients, it is apparent that the future of CER designs will deviate substantially from the traditional approach of evaluating drug A versus drug B. Exploring treatment effect heterogeneity will become central to such evaluations and identifying observable patient characteristics or biomarkers that explains such heterogeneity will increase in popularity. Economic evaluation of technology will look more different than

it currently does, once information regarding heterogeneity is more widely available and understood, and the clinical advantages of basing policy and individual patient decisions on appreciation of heterogeneity in response are recognized.

Disclaimer

A Basu formulated the research question, developed the topical paradigm, defined the statistical method and drafted the manuscript. HY Meltzer participated in the research design, reviewed existing literature and substantially revised the manuscript. Both authors read and approved the final manuscript.

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Executive summary

- Large randomized clinical trials comparing use of antipsychotic drugs have ignored heterogeneity in treatment effects. They tend to prescribe a single answer for all patients and coverage policies.
- Ignoring heterogeneity may have resulted in flawed interpretation of comparative effectiveness research (CER) results for public policy-making.
- A large jump in prior authorization requirements for branded antipsychotic drugs was observed in state Medicaid programs soon after the publication of CATIE results.
- Studies evaluating the effects of such prior authorization requirements have found them to increase costs and plausibly decrease effectiveness, which is contrary to how the CER results were interpreted.
- In many chronic diseases, including schizophrenia, there are many treatment options available that can be used in sequence. CER has the potential to identify optimal navigation processes for patients and insurers by development of effective, dynamic algorithms that can direct treatment decision-making and also inform more efficient access policies.
- Exploring heterogeneity in comparative effects is central to such goals. Going forward, the emerging role of pharmacogenomics and other biomarkers in understanding treatment effect moderation should be the main focus of CER.

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