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When Is Antipsychotic Polypharmacy Supported by Research Evidence? Implications for QI

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Performance Measures

When Is Antipsychotic Polypharmacy Supported by Research Evidence? Implications for QI

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Antipsychotic drugs have demonstrated efficacy and effectiveness for the treatment of schizophrenia and other psychotic disorders.[1] In addition, certain traditional antipsychotics are approved by the Food and Drug Administration (FDA) for treatment of Tourette's syndrome and mania, whereas selected second-generation antipsychotics (SGAs) have additionally received approval for bipolar disorder (manic and maintenance phases) and as adjunctive treatment for treatment-resistant depression.[2–6]

High rates of antipsychotic polypharmacy, defined as the concurrent use of more than one standing antipsychotic drug among patients treated with an antipsychotic, have been observed in numerous studies.[7–28] Rates vary widely, depending on the population, setting, and how polypharmacy is measured. On the basis of the threshold of two or more antipsychotics, studies of acutely hospitalized patients report rates of 30%–40%,[8,9,11,12] whereas studies of outpatient samples (across the Department of Veterans Affairs, Medicaid, and state mental health systems) report rates of 11%–35%.[13,14,16] Less information is available on concurrent use of more than two antipsychotics; one study reported that 4.6% of inpatients were on three or more antipsychotics.[8] Most of these studies lack information on the degree to which use of multiple antipsychotics was clinically appropriate. Medical records typically lack the necessary documentation to make this determination, including the patient's history of previous antipsychotic trials and their outcomes or other rationales for polypharmacy.[29–31]

The extent of antipsychotic polypharmacy has been viewed with mounting concern, resulting in many calls for reducing its use.[15,16,19,32–36] Clinically, antipsychotic polypharmacy has the potential to cause increased side effects and drug interactions. Increasing the number of medications prescribed can lead to a decline in patient adherence.[37,38] Financially, the high cost of SGAs has strained state Medicaid and mental health budgets, leading some states to impose formulary restrictions limiting or delaying their use.[32,34,39,40]

Measurement-based quality improvement (QI) is a method

Article-at-a-Glance

Background: Concurrent use of multiple standing antipsychotics (antipsychotic polypharmacy) is increasingly common among both inpatients and outpatients. Although this has often been cited as a potential quality-of-care problem, reviews of research evidence on antipsychotic polypharmacy have not distinguished between appropriate versus inappropriate use.

Methods: A MEDLINE search from 1966 to December 2007 was completed to identify studies comparing changes in symptoms, functioning, and/or side effects between patients treated with multiple antipsychotics and patients treated with a single antipsychotic. The studies were reviewed in two groups on the basis of whether prescribing was concordant with guideline recommendations for multiple-antipsychotic use.

Results: A review of the literature, including three randomized controlled trials, found no support for the use of antipsychotic polypharmacy in patients without an established history of treatment resistance to multiple trials of monotherapy. In patients with a history of treatment resistance to multiple monotherapy trials, limited data support antipsychotic polypharmacy, but positive outcomes were primarily found in studies of clozapine augmented with a second-generation antipsychotic.

Discussion: Research evidence is consistent with the goal of avoiding antipsychotic polypharmacy in patients who lack guideline-recommended indications for its use. The Joint Commission is implementing a core measure set for Hospital-Based Inpatient Psychiatric Services. Two of the measures address antipsychotic polypharmacy. The first measure assesses the overall rate. The second measure determines whether clinically appropriate justification has been documented supporting the use of more than one antipsychotic medication.

used by hospitals and other provider organizations to assess and improve their clinical practices. QI priorities are often established by external organizations, such as payers or accreditors, by implementing quality measures. Hospitals, for example, are required to report their performance on standardized core measures. External groups then use the results in one or more ways to encourage hospitals to improve, such as providing hospitals with feedback comparing their performance with peer organizations, disclosing results publicly in an effort to influence purchaser or consumer decisions, or linking financial incentives to improved performance.[41]

Two national measurement-based QI initiatives are aimed at decreasing unnecessary antipsychotic polypharmacy. The National Association of State Mental Health Program Directors Research Institute has implemented a measure of antipsychotic polypharmacy rates in a number of state psychiatric hospitals.[35]

Effective October 1, 2008, The Joint Commission is implementing a core measure set for Hospital-Based Inpatient Psychiatric Services; two of the measures address antipsychotic polypharmacy. The first measure assesses the hospital's overall rate. The second measure determines whether clinically appropriate justification has been documented when more than one antipsychotic is used.[36] The Joint Commission initiative is discussed further in the "Discussion" section (pages 579–580).

One factor limiting QI initiatives to reduce antipsychotic polypharmacy has been a lack of clarity about the research evidence regarding its use. Practice guidelines addressing multiple antipsychotic use recommend the addition of a second antipsychotic only after multiple trials of adequate duration of a single antipsychotic.[42–44] However, previous review articles evaluating antipsychotic polypharmacy[45,46] have not distinguished between research studies of patients meeting this criterion and studies of patients who do not.

This article reviews studies comparing outcomes of patients receiving multiple antipsychotics with outcomes of patients receiving antipsychotic monotherapy, first, among patients with documented treatment resistance to multiple trials of a single antipsychotic, and then, among patients without an established history of treatment resistance to monotherapy.

Methods

In January 2008, we conducted a MEDLINE search from 1966 to December 2007 to identify studies comparing changes in symptoms, functioning, and/or side effects between patients treated with multiple antipsychotics and patients treated with a single antipsychotic. The following search terms were used: *antipsychotic, polypharmacy, augmentation, treatment resistance,* *combination, side effects, adverse reactions, quality, measure, improvement, monotherapy, outcomes, multiple antipsychotics.* The reference sections of these articles and previous reviews were searched for articles not identified in the original search. Articles were restricted to the English language. Data on the study design, drugs prescribed, and changes in symptoms, functioning, and side effects were abstracted and reported.

In keeping with guideline recommendations for multiple antipsychotic use,[42–44] we report findings from studies of patients with a documented history of treatment resistance (including partial response) to multiple trials of a single antipsychotic separately from studies of patients without such a history established. We examined studies within strata reflecting the rigor of their study design: randomized controlled trials (RCTs), nonrandomized controlled studies, and noncontrolled observational studies. Because of the robust number of studies with one of these designs, we excluded case reports and series without statistical analyses. Major limitations of each study are noted in the evidence tables; these include small sample sizes in some studies, limited matching characteristics, and short periods before follow-up assessment. Unless otherwise noted, all comparisons reported were statistically significant.

Results

SAMPLES WITH ESTABLISHED TREATMENT RESISTANCE TO ANTIPSYCHOTIC MONOTHERAPY

We identified six RCTs comparing antipsychotic polypharmacy to monotherapy in samples with established treatment resistance to trials of a single antipsychotic (Table 1, pages 573–575).[47–52] All studies were of patients with schizophrenia or schizoaffective disorder. Two studies found that patients on multiple antipsychotics, compared with patients on a single antipsychotic, experienced greater improvement in the primary clinical outcome (that is, symptoms or functioning).[50,52] Three trials found no difference in the primary clinical outcome between patients on single and multiple antipsychotics.[48,49,51] One trial reported better clinical outcomes for patients on a single antipsychotic.[47] Four of the six trials reported comparatively greater side effects for patients on multiple antipsychotics, whereas two found no differences in side effects.[47–49,52] One trial reported that risperidone augmentation of clozapine worsened verbal working memory, while this outcome improved in the group that remained on a single antipsychotic.[47]

The RCTs had small sample sizes (16–68 patients), were relatively brief (lasting from 6 to 12 weeks), and focused on a narrow selection of antipsychotics. Five of the six trials examined antipsychotic augmentation of clozapine.[47–50,52] In four trials, the

Table 1. Studies Comparing Multiple Antipsychotics to Antipsychotic Monotherapy Among Patients with Established Treatment Resistance to Monotherapy*

Reference	Design	Clinical Outcomes	Side Effects/Adverse Events	Comments
Randomized Clinical Trials (RCTs) Comparing Multiple Antipsychotics to Monotherapy				
Anil-Yağcioğlu[47] 2005	Double blind (DB) RCT comparing clozapine with clozapine/risperidone patients with schizophrenia partially responsive to clozapine monotherapy	■ Monotherapy led to greater improvement in positive symptoms overall on PANSS (p = .02; primary outcome). ■ Monotherapy led to greater improvement in delusions. ■ No difference between groups in quality of life or functioning	■ Multiple antipsychotics increased sedation (p = .01). ■ Multiple antipsychotics increased prolactin levels ($p \leq$ .0001). ■ No increase in QTc with combination	
Freudenreich[48] 2007	DB RCT comparing clozapine with clozapine/risperidone in patients with stable residual symptoms of schizophrenia	■ No difference between groups in symptom improvement on PANSS (primary outcome) ■ Multiple antipsychotics led to greater improvement in disorganized thought subscale (p = .047).	■ Multiple antipsychotics increased prolactin levels (p = .02). ■ Multiple antipsychotics led to tachycardia (significant but no p value given).	
Honer[49] 2006	DB RCT comparing clozapine with clozapine/risperidone in patients with schizophrenia and schizoaffective disorder poorly responsive to clozapine monotherapy	■ No difference between groups in symptom improvement on PANSS (primary outcome) ■ No difference between groups in number of responders ■ Multiple antipsychotics led to worsening in verbal working memory compared with monotherapy (p = .02).	■ Multiple antipsychotics increased fasting blood glucose (p < .04).	■ Response defined as $\geq$ 20% decrease in symptoms
Josiassen[50] 2005	DB RCT comparing clozapine with clozapine/risperidone in patients with schizophrenia and schizoaffective disorder unresponsive or partially responsive to clozapine monotherapy	■ More patients responded on combination (p < .01; primary outcome). ■ Both groups experienced a reduction of symptoms on BPRS (p < .0001). ■ Combination more effective at symptom reduction than monotherapy (p < .04).	■ No difference in side effects including weight, agranulocytosis, and seizures	■ Response defined as $\geq$ 20% decrease in symptoms on BPRS
Kotler[51] 2004	RCT comparing olanzapine with olanzapine/sulpiride in patients with treatment-resistant schizophrenia receiving olanzapine monotherapy	■ No difference between groups in psychotic and anxiety symptom improvement on PANSS (primary outcome). ■ Multiple antipsychotics led to improvement in depressive symptoms on HAMD (p < .05).	■ No difference in extrapyramidal side effects or weight	
Shiloh[52] 1997	DB RCT comparing clozapine with clozapine/sulpiride in patients with schizophrenia partially responsive to clozapine monotherapy	■ Multiple antipsychotics led to significant improvement in symptoms on BPRS (p < .05; primary outcome). ■ Multiple antipsychotics led to significant improvement in positive symptoms on SAPS (p < .05). ■ Multiple antipsychotics led to significant improvement on negative symptoms on SANS (p < .05). ■ More patients responded in combination treatment group (p < .02).	■ Multiple antipsychotics increased prolactin levels 4-to-7-fold (p < .05).	■ Response defined as $\geq$ 20% decrease in symptoms
Observational, Noncontrolled Studies of Augmentation of Monotherapy to Multiple Antipsychotic				
Agelink[53] 2004	Open-label, observational study of amisulpride added to clozapine for psychosis or schizoaffective disorder unresponsive to clozapine monotherapy	■ Multiple antipsychotics led to greater improvement in symptoms on BPRS (p < .05; primary outcome).	■ No changes in ECG in either group	

Table 1. Studies Comparing Multiple Antipsychotics to Antipsychotic Monotherapy Among Patients with Established Treatment Resistance to Monotherapy* (continued)				
Reference	**Design**	**Clinical Outcomes**	**Side Effects/Adverse Events**	**Comments**
Observational, Noncontrolled Studies of Augmentation of Monotherapy to Multiple Antipsychotic				
de Groot[54] 2001	Open-label, observational study of risperidone added to clozapine for patients with persistent symptoms of schizophrenia despite treatment with clozapine monotherapy	■ No patients responded to treatment with multiple antipsychotics on PANSS (*n* = 11).	■ No changes in extrapyramidal side effects or labs ■ 1 dropout due to orthostatic hypotension	■ Response defined as ≥ 20% symptom reduction
Friedman[55] 1997	Retrospective case review of the addition of pimozide in patients partially responsive to clozapine with schizophrenia or schizoaffective disorder	■ Multiple antipsychotics led to greater improvement in symptoms on BPRS (*p* = .03; primary outcome).	■ Not reported	
Henderson[56] 1996	Open-label, observational study of risperidone added to clozapine for residual symptoms of schizophrenia and schizoaffective disorder	■ Multiple antipsychotics led to greater improvement in symptoms on BPRS (*p* = .0002). ■ Multiple antipsychotics led to greater reduction in positive symptoms on BPRS (*p* = .001). ■ Multiple antipsychotics led to greater reduction in negative symptoms on BPRS (*p* = .004). ■ Multiple antipsychotics led to greater reduction in depressive symptoms on BPRS (*p* = .02).	■ Worsened akathisia (33%) hypersalivation with (42%) multiple antipsychotics (NS) ■ 1 increased fatigue vs. 6 decreased fatigue following augmentation (NS)	
Megna[57] 2007	Retrospective chart review of patients treated with single atypical antipsychotic for at least 4 months followed by addition of second agent for severe persistent schizophrenia or schizoaffective disorder	■ 26% average reduction in symptoms following treatment with multiple antipsychotics on BPRS (*p* = .016).	■ Increased use of side effect medications following multiple antipsychotics (*p* < .04)	■ Decreased use of PRN antipsychotics following augmentation of standing regimen to multiple antipsychotics (*p* < .04) ■ No patients improved sufficiently to be discharged
Munro[58] 2004	Open-label, observational study of amisulpride added to clozapine partial or nonresponders with schizophrenia	■ Multiple antipsychotics led to greater improvement in symptoms on PANSS, SANS, GAF, BPRS (*p* < .0001). ■ Depression and anxiety did not improve with multiple antipsychotics.	■ Multiple antipsychotics significantly elevated prolactin (*p* < .0001).	
Taylor[59] 2001	Open-label, observational study of risperidone augmentation of clozapine for patients with schizophrenia and schizoaffective disorder partially responsive to clozapine	■ Significant improvement in symptoms with combination on PANSS (*p* = .0002) ■ Significant improvement in symptoms with combination in positive (*p* = .0003), negative (*p* = .0004), and general psychopathology (*p* = .0007)	■ One patient had worsening of compulsive behaviors.	
Ziegenbein[60] 2006	Open-label, observational study of aripiprazole augmentation of clozapine for treatment-resistant schizophrenia	■ Significant improvement in symptoms with combination on BPRS (*p* < .05)	■ Increased side effects over the first two weeks of the multiple antipsychotics that resolved over time ■ No significant QTc changes with multiple antipsychotics	■ Clozapine doses were lowered an average of 16%.

Table 1. Studies Comparing Multiple Antipsychotics to Antipsychotic Monotherapy Among Patients with Established Treatment Resistance to Monotherapy* (continued)				
Reference	**Design**	**Clinical Outcomes**	**Side Effects/Adverse Events**	**Comments**
Observational, Noncontrolled Studies of Augmentation of Monotherapy to Multiple Antipsychotic				
Ziegenbein[61] 2005	Open-label, observational study of ziprasidone-clozapine combination for treatment-resistant schizophrenia	■ Significant improvement in symptoms with combination on BPRS (p = .013)	■ Side effects reported with multiple antipsychotics: 2 patients each with increased sedation, decreased sedation, hypersalivation, weight loss; 1 patient each with increased LFTs, tremor, EEG changes; hypotension (all NS)	■ Multiple antipsychotics accompanied by 18% reduced total daily dose of clozapine

* PANSS, Positive and Negative Syndrome Scale; QTc, Q-T interval corrected for heart rate; BPRS, Brief Psychiatric Rating Scale; HAMD, Hamilton Depression (Scale); SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; ECG, electrocardiogram; NS, not significant; PRN, as needed; GAF, Global Assessment of Functioning (Scale); LFTs, liver function tests; EEG, electroencephalogram.

augmenting agent was risperidone,[47–50] whereas in the fifth it was sulpiride[52], an SGA not available in the United States. The sixth trial compared the combination of olanzapine and sulpiride with olanzapine monotherapy.[51]

We identified nine noncontrolled observational trials comparing antipsychotic polypharmacy to monotherapy in samples with established treatment resistance to trials of a single antipsychotic (Table 1).[53–61] All studies were of patients with schizophrenia or schizoaffective disorder. Eight of the trials reported significant improvement in reduced symptoms with the addition of a second antipsychotic.[53,55–61] Of the eight studies that examined side effects, four reported no change with the addition of a concurrent antipsychotic.[53,54,59,60] Three studies reported increased side effects with the addition of another antipsychotic,[56–58] whereas one study reported a decrease in sedation.[56]

The observational studies also had small sample sizes (7–28 patients), and most of them were longer than the RCTs (1–9 months). As with the more rigorous trials, these studies focused on a narrow selection of antipsychotics. Of the nine trials, eight involved clozapine augmentation.[53–56,58–61] Clozapine was augmented with risperidone in three studies;[54,56,59] amisulpride (a second-generation drug not available in the United States) in two trials;[53,58] and pimozide[55], aripiprazole,[60] and ziprasidone[61] each in one trial. The ninth trial reported on the nonspecific use of two SGAs in combination.[57]

SAMPLES WITHOUT ESTABLISHED TREATMENT RESISTANCE TO ANTIPSYCHOTIC MONOTHERAPY

We identified three RCTs that compared antipsychotic polypharmacy to monotherapy in samples *without* established treatment resistance to a single antipsychotic (Table 2, pages 576–578).[60–62] All three studies were of patients with schizophrenia or schizoaffective disorder. None of the three trials found clinical outcomes from multiple antipsychotics to be significantly better than outcomes from a single antipsychotic.[62–64] Of the two trials that studied side effects, one[62] reported worsened constipation and sedation in the multiple-antipsychotic group, while the other[64] reported reduced prolactin levels with aripiprazole augmentation.

We identified six nonrandomized controlled trials that compared antipsychotic polypharmacy to monotherapy in samples without established treatment resistance to a single antipsychotic (Table 2).[65–70] Three of the trials studied samples with mixed diagnoses,[65–67] whereas three studied schizophrenia or schizoaffective disorder.[68–70] Of the four trials reporting clinical outcomes, three reported no improvement,[65,66,69] while the fourth study reported mixed results.[70] Multiple antipsychotics were more beneficial than monotherapy at lower dosages but no better than monotherapy at higher dosages.[70] Four of the six studies reported on side effects—three reported a trend toward greater side effects with multiple antipsychotics[66,68,70] and the fourth reported significantly greater side effects in this group.[68]

We identified six noncontrolled observational studies that examined the relationship between antipsychotic polypharmacy and clinical outcomes in samples without documented treatment resistance to monotherapy (Table 2).[71–76] One study did not report on clinical outcomes.[71] Three of the studies evaluated the addition of a second antipsychotic to an existing antipsychotic[72,74,75]; two studies found no improvement in

Table 2. Studies Comparing Multiple Antipsychotics to Antipsychotic Monotherapy Among Patients Without Established Treatment Resistance to Monotherapy

Reference	Design	Clinical Outcomes	Side Effects/Adverse Events	Comments
Randomized Controlled Trials (RCTs) Comparing Multiple Antipsychotics to Monotherapy				
Potkin[62] 2002	An open-label RCT comparing quetiapine alone in initial period with quetiapine combination (randomly assigned to haloperidol, risperidone, or thioridazine) for patients in remission from psychotic symptoms in schizophrenia, bipolar, or schizoaffective disorder	■ No significant differences in symptom change between multiple-antipsychotic groups and monotherapy group on BPRS or CGI	■ Risperidone + quetiapine increased sleepiness ($p < .05$). ■ Haloperidol + quetiapine increased constipation ($p < .05$).	■ Study's primary intent was to assess for drug interactions; also examined clinical outcomes and other side effects. ■ Short study period: initial monotherapy phase of ≥ 7 days, followed by combination phase of 8.5 days
Potter[63] 1989	RCT of chlorpromazine alone, clozapine alone, or chlorpromazine + clozapine for schizophrenia	■ Multiple antipsychotics were no better than monotherapy with clozapine in reducing overall symptom levels on BPRS.	■ Not reported	■ Clozapine with or without chlorpromazine was more effective in reducing selected positive symptoms than chlorpromazine alone.
Shim[64] 2007	Double blind (DB) RCT of augmentation of haloperidol with aripiprazole for patients with hyperprolactinemia on haloperidol for clinically stable schizophrenia.	■ No significant change in symptoms observed with augmentation on BPRS	■ Prolactin normalized on haloperidol-aripiprazole ($p < .0001$; primary outcome) ■ Dry mouth (31%), headache (23%), insomnia (42%), and weakness occurred more frequently in augmentation group (NS). ■ EPS improvement in 20% of augmented patients (NS) ■ 2 patients withdrew because of insomnia, irritability, and anxiety on combination.	■ Study's primary intent was to assess potential of augmentation to lower prolactin levels; also examined clinical outcomes and other side effects.
Nonrandomized Controlled Studies Comparing Multiple Antipsychotics to Monotherapy				
Centorrino[65] 2005	Retrospective matched control trial comparing hospitalized patients treated with multiple antipsychotics or monotherapy for mixed diagnoses	■ Multiple antipsychotics were no better than monotherapy for symptom reduction on PANSS, CGI, GAF.	■ Not reported	■ Total antipsychotic dose 2.1 times greater with multiple antipsychotics compared with monotherapy ($p = .005$) ■ Matching based on age, gender, diagnosis, and admission clinical ratings ■ Patients on multiple antipsychotics had more positive symptoms at admission and discharge compared with monotherapy ($p < .0001$; $p = .002$).

Table 2. Studies Comparing Multiple Antipsychotics to Antipsychotic Monotherapy Among Patients Without Established Treatment Resistance to Monotherapy (continued)				
Reference	**Design**	**Clinical Outcomes**	**Side Effects/Adverse Events**	**Comments**
Nonrandomized Controlled Studies Comparing Multiple Antipsychotics to Monotherapy				
Centorrino[66] 2004	Retrospective matched control trial comparing patients treated with multiple antipsychotics or monotherapy for mixed diagnoses	■ Multiple antipsychotics were no better than monotherapy for symptom reduction on PANSS, CGI, and GAF.	■ Higher adverse events with multiple antipsychotics (NS) ■ Risk of additional medication for EPS was 40% with multiple antipsychotics compared with 25.7% with monotherapy (NS). ■ Adverse events higher with higher total daily doses	■ Total daily dose of antipsychotic 78% higher with multiple antipsychotics ($p < .001$) ■ Length of stay longer with APP ($p < .001$)
Correll[67] 2007	Cross-sectional study of multiple antipsychotics with at least one atypical compared with atypical antipsychotic monotherapy on risk of metabolic syndrome in mixed diagnoses	■ Not reported	■ Risk of metabolic syndrome was not significantly higher with multiple antipsychotics compared with monotherapy in multivariate analysis controlling for clinical and sociodemographic factors.	
Henderson[68] 2001	Matched case control study examining effects on prolactin levels of risperidone added to clozapine compared with clozapine alone for schizophrenia	■ Not reported	■ Multiple antipsychotic use associated with significant increases in prolactin, weight, and BMI compared with monotherapy ($p < .0001$, $p = .0296$, $p = .0273$)	■ Matched for age and gender only
Knight[69] 1979	DB controlled crossover trial comparing thiothixene with combination of trifluoperazine and chlorpromazine for schizophrenia	■ Multiple antipsychotics were no better than monotherapy for symptom or behavioral improvement on BPRS	■ Increased side effects with combination (NS)	
Nishikawa[70] 1985	Controlled trial comparing combination of pimozide and thioridazine with each drug individually to prevent reemergence of symptoms in asymptomatic patients with schizophrenia	■ Mixed results based on dosage of monotherapy agents. Multiple antipsychotics associated with more symptom-free days in comparison to lower-dose monotherapy groups but not significantly different in comparison to higher-dose monotherapy groups.	■ Signs of "overdose" more common with combination	■ Patients not matched but similar at baseline
Noncontrolled Studies Comparing Multiple Antipsychotics to Monotherapy				
Ganesan[71] 2007	Retrospective study comparing multiple antipsychotics to monotherapy for mixed diagnoses	■ Not reported	■ No difference in side effects between groups on UKU	■ Monotherapy patients on more antidepressants ($p < .001$)
Henderson[72] 2006	Prospective observational study of the effects of aripiprazole added to clozapine for schizophrenia	■ Multiple antipsychotics did not significantly improve average symptom levels compared with monotherapy on PANSS	■ Significant decreases in weight and BMI, cholesterol, TG, HDL, and fatigue with addition of aripiprazole ($p = .003$, $p = .004$, $p = .002$, $p = .04$, $p = .015$)	

Table 2. Studies Comparing Multiple Antipsychotics to Antipsychotic Monotherapy Among Patients Without Established Treatment Resistance to Monotherapy (continued)				
Reference	Design	Clinical Outcomes	Side Effects/Adverse Events	Comments
Noncontrolled Studies Comparing Multiple Antipsychotics to Monotherapy				
Joukamaa[73] 2006	Retrospective observational study of mortality in patients treated with 0, 1, 2, or ≥ 3 antipsychotics for schizophrenia	■ Relative risk for death per increment of each additional antipsychotic was 2.5 (95% CI, 1.46–4.30).	■ HDL decreased associated with combination ($p < .001$)	■ 17-year study with group assignment based on number of antipsychotics at baseline ■ Multivariate analysis adjusting for age, gender, somatic diseases, lifestyle, and risk factors (i.e., smoking, exercise, alcohol, body mass index, level of education)
Reinstein[74] 1999	Retrospective study of patients who developed diabetes on clozapine monotherapy and were switched to clozapine-quetiapine combination for schizophrenia	■ No adverse behavioral changes with addition of quetiapine	■ Mean weight loss 9.2 lbs. ($p < 0.001$) ■ Improved diabetes ($p < .001$)	
Tapp[75] 2005	Retrospective study of the effect of addition of a second antipsychotic compared with monotherapy for psychotic disorders	■ Treatment with multiple antipsychotics did not improve symptoms compared with monotherapy on PANSS.	■ Clinician ratings of EPS were unchanged with the addition of second antipsychotic on ESRS. ■ Patient's subjective reports of EPS significantly increased by 22% with addition of second antipsychotic.	
Waddington[76] 1998	Prospective observational study of mortality in patients diagnosed with schizophrenia at a long-term inpatient facility	■ Relative risk of death among patients treated with multiple antipsychotics was 2.46 (95% CI, 1.10–5.47; $p = .03$).	■ Not reported	■ 10-year study with group assignment based on maximum number of antipsychotics prescribed concurrently ■ Other risk factors associated with earlier death were edentulousness, absence of treatment with anticholinergic medications, and time since last antipsychotic treatment

* BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression (Scale); EPS, extrapyramidal side affects; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning (Scale); BMI, body mass index; NS, not significant; UKU, The Udvalg for Kliniske Undersøgelser Side Effect Rating Scale; TG, triglycerides; HDL, high-density lipoprotein; CI, confidence interval; ESRS, Extrapyramidal Symptoms Rating Scale.

symptoms,[72,75] while one study reported no clinical effects.[74] The remaining two studies had a different design, using regression analysis to assess the association between antipsychotic polypharmacy and premature death in patients with schizophrenia.[73,76] Controlling for multiple sociodemographic and clinical factors, both studies found that use of two or more antipsychotics was associated with increased mortality. Five of the six studies reported on side effects.[71–75] Two found that antipsychotic polypharmacy was associated with improved side effects,[72,74] one with worsening,[73] and the other with no difference.[71,75]

Discussion

Despite the high prevalence of antipsychotic polypharmacy, the

The Joint Commission's Hospital-Based Inpatient Psychiatric Service (HBIPS) Core Measures on Antipsychotic Polypharmacy

1. Patients discharged on multiple antipsychotic medications

Denominator: Psychiatric inpatients discharged on one or more routinely scheduled antipsychotic medications
  Standing antipsychotics only
  Planned discharges only

Numerator: Inpatients from the denominator who are discharged on two or more routinely scheduled antipsychotic medications

2. Patients discharged on multiple antipsychotic medications with appropriate justification

Denominator: Psychiatric inpatients discharged on two or more routinely scheduled antipsychotic medications
  Standing antipsychotics only
  Planned discharges only

Numerator: Inpatients from the denominator discharged on two or more routinely scheduled antipsychotic medications with appropriate justification, i.e., is there documentation in the medical record of:
  A history of three or more failed trials of monotherapy
  Recommended plan to taper to monotherapy in continuing care plan
  Clozapine augmentation

Figure 1. *The core measures are shown, along with denominators and numerators. Source: The Joint Commission:* Specification Manual for National Quality Measures––Hospital Based Inpatient Psychiatric Services Psychiatric Core Measure Set (Version 2.0a). *Jul. 2008.* http://www.jointcommission.org/PerformanceMeasurement/PerformanceMeasurement/Hospital+Based+Inpatient+Psychiatric+Services.htm (last accessed Aug. 20, 2008).

data in support of this practice are limited and narrowly focused. Among patients with established treatment resistance to previous trials of antipsychotic monotherapy, RCTs showed mixed results in clinical outcomes and generally greater side effects with multiple antipsychotics. Positive clinical findings were limited to studies that either included SGAs unavailable in the United States or augmentation of clozapine, a unique antipsychotic with relative low utilization in the United States because of risks of agranulocytosis and need for close monitoring.[62–64] The findings support wider use of clozapine, which practice guidelines recommend be tried before use of multiple antipsychotics.[42–44] The findings also emphasize the need for further research on augmentation strategies using a wider range of antipsychotics.

On the other hand, among patients who do not meet the guideline recommendation of multiple unsuccessful trials of a single antipsychotic before the addition of a second, research studies do not support use of multiple antipsychotics. Three RCTs and five of six nonrandomized controlled trials found multiple antipsychotics to be no better than a single antipsychotic in improving primary clinical outcomes. The sixth controlled trial showed mixed results based on dose. Data on side effects were limited in these studies but generally suggested that polypharmacy was associated with greater side effects.

In both groups, studies with more rigorous designs (that is, RCTs and other controlled studies) were more likely to show a lack of benefit from polypharmacy than studies with less rigorous designs. A limitation of these trials is that few studies confirmed patient adherence, either through blood levels or other means, with antipsychotic medications as prescribed.

In light of concern over the high prevalence of antipsychotic polypharmacy and the evidence from research studies, the Joint Commission has adopted two measures of antipsychotic polypharmacy as part of its recently issued core measure set for Hospital-Based Inpatient Psychiatric Services (HBIPS; Figure 1, left).[36] The first measure reports hospitals' rate of patients discharged on two or more routinely scheduled antipsychotics. The second examines whether patients discharged on two or more antipsychotics have a documented, clinically appropriate justification for use of multiple agents.

In developing these and the five other HBIPS measures, the Joint Commission brought together a technical advisory panel[36] representing a range of stakeholder perspectives. Part of the panel's role was to identify clinically appropriate justifications for multiple antipsychotics. The first two justifications come directly from practice guidelines and research studies: a history of multiple unsuccessful trials of monotherapy and augmentation of clozapine. The third justification reflects a reality of contemporary inpatient psychiatric care. In this era of short inpatient stays, the primary focus of hospitalization for acute episodes of psychotic conditions is stabilization, followed by transfer to a less intensive level of care for ongoing treatment. Under these circumstances, inpatient clinicians often add a new antipsychotic to an existing one but discharge the patient before the original antipsychotic can be safely tapered off. Among patients who have not had multiple trials of monotherapy, discontinuation of the initial agent can be completed by

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the provider of the next level of care. Thus, the third clinically appropriate rationale built into the measure is as follows: documented communication to the patient's after-care clinician of a continuing care plan recommending a taper to monotherapy.

The advisory panel considered other reasons that psychiatrists may have for prescribing multiple antipsychotics, including those proposed in Joint Commission focus groups and in response to calls for public comment. No other rationales were adequately supported by research evidence or by consensus judgments of expert clinicians.

Reducing unnecessary antipsychotic polypharmacy poses several challenges to inpatient psychiatric units and the hospital systems that support them. Documentation of a patient's past antipsychotic trials often is missing or incomplete, or is spread over several volumes of old medical records. Improving performance will likely require that inpatient units adopt systematic processes to maintain accessible, up-to-date information on previous antipsychotic treatment—including documentation of past drug trials and their duration, clinical response, and side effects. Another challenge is that communication between inpatient and outpatient clinicians following a hospital stay varies widely.[77] Although discharge summaries are routinely completed at or near time of discharge, they often are not sent to providers at the next level of care in a timely fashion. Patients with psychotic illnesses can be a limited conduit for providing treatment plan information and may or may not have family members, case managers, or others who serve this role. Improving communication between hospital and providers of the next level of care is the primary goal of another HBIPS measure and is an important component of avoiding unnecessary antipsychotic polypharmacy by communicating the inpatient psychiatrist's intentions regarding antipsychotic medications.

A final challenge is not limited to this quality measure but is common to all QI activities based on process measures that can be influenced by multiple providers, clinical settings, and patients themselves. Will inpatient clinicians and managers be able to focus on and act on that part of unnecessary antipsychotic polypharmacy that *is* under their control, as opposed to that which is determined by others? It is unlikely that even the most evidence-based, conscientious, and effective inpatient units will achieve perfect performance on even the second measure, any more than adult inpatient units can truly reduce restraint rates to zero if they admit agitated, assaultive psychotic patients. However, just as many facilities, including state mental health systems, have achieved significant decreases in physical restraint use through education, training, innovative procedures, and enhanced communication,[78,79] it is likely that inpatient teams can also reduce the rate of unnecessary antipsychotic polypharmacy.

Several interventions to reduce multiple antipsychotic use have achieved promising results. For example, Suzuki et al. converted 22 of 44 patients (initially treated with an average of three antipsychotics) to a single antipsychotic. Of the 22 patients on monotherapy, 8 showed symptomatic improvement, whereas symptom levels for the other 14 were unchanged.[80] Dissemination of treatment algorithms alone has not been found to be effective,[16] but Chong et al. reported that combining treatment algorithm implementation with periodic audits of algorithm compliance significantly decreased antipsychotic polypharmacy.[19] Thompson et al. achieved a modest reduction using a multifaceted approach combining group education, academic detailing, and chart reminders. The literature on interventions to reduce antipsychotic polypharmacy is extensive; review of these studies would be timely. In addition, rigorously designed trials evaluating current best practices would be of value to inpatient clinicians and managers.

While we have chosen to focus this review on the clinical impact of antipsychotic polypharmacy, other authors have described the financial impact of this practice.[81,82] Financial concerns have led many payers to implement formulary restrictions on antipsychotic use. These restrictions are often more sweepingly restrictive than evidence-based guideline recommendations for multiple antipsychotic use.[83]

Conclusion

Research evidence only supports the use of antipsychotic polypharmacy in treatment-resistant patients, primarily when augmenting clozapine with an SGA. Treatment guidelines recommend not resorting to antipsychotic polypharmacy until after multiple failed trials of antipsychotic monotherapy, including clozapine. Ultimately, the value of assessing and reducing rates of antipsychotic polypharmacy requires the demonstration of improved clinical outcomes and/or reduced side effects after converting patients from multiple, unjustified antipsychotics to monotherapy. Ideally, this should be done through RCTs that provide definitive evidence of causality. However, the implementation of a nationwide quality measure offers an excellent, naturalistic opportunity to validate the measure by examining the association between improved performance and patient outcomes. Further research is also needed to identify the most effective (and cost-effective) methods for achieving improved performance. **J**

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