Recent Trends in Antipsychotic Combination Therapy of Schizophrenia and Schizoaffective Disorder: Implications for State Mental Health Policy

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Abstract

Little is known about antipsychotic combination therapy, although this practice is becoming increasingly common in the treatment of schizophrenia. Medicaid pharmaceutical claims for a cohort of 836 New Hampshire beneficiaries with schizophrenia or schizoaffective disorder were followed from 1995 through 1999. Use of traditional and atypical antipsychotic medications, antidepressants, anxiolytic hypnotics, and mood stabilizers was tracked monthly. The number of medications, frequency of coprescription, and Medicaid pharmaceutical costs are described. The proportion of individuals with schizophrenia and schizoaffective disorder treated with atypical antipsychotics grew from 43 percent in 1995 to 70 percent in 1999. At the same time, concurrent use of two or more antipsychotic medications quadrupled, increasing from 5.7 percent to 24.3 percent. Persons with schizophrenia were also prescribed more antidepressants (increased from 18.5% in 1995 to 35.6% in 1999), anxiolytics (increased from 19.9% to 33.5%), and mood stabilizers (increased from 17.7% to 30.0%). The increase in multiple agent therapy appears to be broad-based. Data are needed on the effectiveness and cost-effectiveness of these practices to inform clinical decision making and health policy.

Keywords: Schizophrenia, schizoaffective, polypharmacy, combination therapy, atypical antipsychotics.


Combination therapy with antipsychotic medications is being embraced as an increasingly common practice by clinicians in the treatment of schizophrenia, yet there is a surprising lack of data documenting this trend or supporting its effectiveness. Early reports describe combination therapy with high- and low-potency neuroleptics as a strategy to balance side effects while maintaining efficacy (Davidson 1974; Godleski et al. 1989). More recently, combination therapy using atypical antipsychotic agents has gained new currency among clinicians as a means to optimize outcomes for treatment-resistant or residual symptoms, including combinations of atypical and typical antipsychotics or combinations of two atypical antipsychotic drugs (Canales et al. 1999; Stahl 1999a; Meltzer and Kostakoglu 2000). Despite increasing acceptance of antipsychotic combination therapy, there is only one controlled study evaluating the effectiveness of this practice (Shiloh et al. 1997).

The lack of an evidence base for combination therapy is especially challenging for State mental health authorities and clinical administrators who are responsible for justifying Medicaid pharmacy costs, one of the most rapidly growing components of the public health care budget. In recent years, psychiatric medications, including atypical antipsychotics and selective serotonin reuptake inhibitors (SSRIs), have accounted for seven of the ten most expensive medications purchased through State Medicaid plans (unpublished New Hampshire Medicaid data). State mental health authorities around the country are being asked to develop strategies for controlling spending on antipsychotics, and some are having such strategies imposed on them. Data are needed on the trends and patterns of combination therapy in the treatment of schizophrenia in order to inform health policy. This article provides a detailed description of this trend by examining the use of combination therapy in a cohort of Medicaid beneficiaries over 5 years of treatment.

Coprescription—sometimes called polypharmacy—is increasing in clinical practice, although the extent of or reasons for such a trend are not well documented (Stahl 1999b; Meltzer and Kostakoglu 2000). A common explanation for the increasing use of combination therapy in...
schizophrenia treatment is that different types and classes of agents have different and complementary affinities for different receptors that play a role in psychosis. For example, the scientific rationale for combining traditional neuroleptics with atypical antipsychotic drugs includes complementing the D2 receptor blockade of neuroleptics with atypical agents that have varying affinities for different 5-HT receptors. A review of three prescription surveys found that up to one-fourth of patients in outpatient settings (diagnosis not specified) receive two antipsychotics, usually a neuroleptic and an atypical antipsychotic (Stahl 1999b).

Despite reports of the widespread use of antipsychotic combination therapy by clinicians, the evidence base for this practice (with the exception of a single study) is limited to anecdotal case reports and small, uncontrolled studies. These studies include reports of the addition of thioridazine to risperidone to reduce anxiety and agitation (Goss 1995); the addition of risperidone to traditional neuroleptics for treatment-refractory schizophrenia (Bacher and Kaup 1996); and the combination of low-dose traditional neuroleptics (e.g., haloperidol, trifluoperazine, fluphenazine) with different atypical antipsychotics (risperidone, olanzapine, and quetiapine) for treatment-refractory psychosis (Waring et al. 1999). Combination therapy, including the addition of parenteral traditional neuroleptics to atypical antipsychotics, has also been advocated for crisis management in the treatment of acute psychosis (Ereshefsky 1999), although this practice has been criticized for introducing the risk of acute dystonic reactions with minimal (if any) reduction in time to treatment response (Meltzer and Kostakoglu 2000). The addition of other atypical antipsychotics to clozapine has been described as a means of augmentation therapy in a variety of open trials, including trials combining clozapine with risperidone (McCarthy and Terkelsen 1995; Henderson and Goff 1996; Morera et al. 1999; Raskin et al. 2000) and augmenting clozapine with olanzapine (Gupta et al. 1998). Remarkably, there is only one double-blind, controlled study of the effectiveness of antipsychotic combination therapy. This study of 28 patients with a partial treatment response to clozapine found improvement in positive and negative symptoms for augmentation with sulphiride compared to placebo (Shiloh et al. 1997). Overall, the evidence base for prescribing more than one antipsychotic has not yet been established, and the potential (but unproven) benefits of this practice should be balanced with the increased risk of adverse side effects, the greater likelihood of treatment noncompliance, and the increased pharmacy costs (Lehman and Steinwachs 1998; Meltzer and Kostakoglu 2000; Sherman 2001).

Despite the benefits of atypical antipsychotics, the high use and costs of these medications are attracting attention (Zito 1998; Geddes et al. 2000; Martin et al. 2001). Scrutiny is likely to be further heightened by trends suggesting that clinical practice is moving toward combinations of atypical antipsychotics (Sherman 2001) or combinations of atypical antipsychotics with other relatively expensive agents such as SSRIs. Although cost-effectiveness, rather than cost, is the most appropriate basis for allocating health care expenditures, costly treatments inevitably attract the attention of policy makers seeking to curb public spending. From a health policy perspective, detailed information is needed by State mental health authorities on current prescribing trends to help to define targets for treatment effectiveness research and clinical practice improvement. The purpose of this article is to examine trends in combination therapy in the treatment of schizophrenia and to address the following specific questions:

- What are the magnitude and nature of the recent increase in combination therapy? In view of the long tradition of combination therapy in schizophrenia treatment, to what extent is there a recent increase in this practice, and what combinations are most commonly used by practitioners?
- Is the increasing use of combination therapy a selective and targeted practice consisting of one or two types of antipsychotic combinations? Or is it a trend toward broad-based polypharmacy, including an increase in combinations of antipsychotics with a variety of other antipsychotics, antidepressants, anxiolytics, and mood-stabilizing agents?

### Methods

**Sample.** We used 1995 paid Medicaid claims for New Hampshire beneficiaries with disabilities to identify a cohort of persons with schizophrenia and schizoaffective disorder. Filled prescriptions for this group were then tracked on a monthly basis over the subsequent 5 years beginning January 1, 1995, and ending December 31, 1999. This approach allowed us to identify trends in prescription drug use for a fixed group of persons without risk of bias associated with substantial changes in case mix. In particular, we were interested in eliminating the possibility that an increase in the use of combination therapy might be associated with the entry of new individuals into the treatment system with greater acuity, comorbidity, and treatment complexity. Changes in prescriptions for a single treatment cohort over time are most likely to be associated with evolving treatment practices rather than fluctuations in the clinical complexity and treatment needs of the population being served. Inclusion criteria were as follows: a claims-based diagnosis of schizophrenia or schizoaffective disorder; absence of recorded diagnoses of Alzheimer’s disease, dementia, or mental retardation; and
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Procedures. All paid Medicaid claims in 1995 were used to identify beneficiaries with schizoaffective disorder or schizophrenia diagnoses. Persons with both schizophrenia and schizoaffective disorder during the year were classified as having schizoaffective disorder. Prescription drug claims were followed for the entire 5 years. Medications were classified in four major categories and varying numbers of subcategories (in parentheses): antipsychotics (traditional neuroleptics, including chlorpromazine, haloperidol, trifluoperazine, fluphenazine; and atypical antipsychotics, including clozapine, risperidone, olanzapine, quetiapine), antidepressants (traditional [monoamine oxidase inhibitors and tricyclics]; SSRIs; other novel compounds such as bupropion, venlafaxine, nefazodone, mirtazapine), anxiolytics (e.g., lorazepam, clonazepam), and mood stabilizers (lithium, valproate, carbamazepine, gabapentin, lamotrigine, topiramate). Use of antiparkinsonian drugs to treat extrapyramidal side effects was also monitored. Filled prescriptions for patients were summarized monthly for 5 years. We used point prevalence measures of prescriptions filled in December of each year to describe changes in medication treatment patterns from year to year.

We calculated the number of different medications prescribed in a month and the length of time over which a given combination of antipsychotic medications was prescribed, choosing a conservative cutoff point of 9 months to distinguish between within-class coprescription during a medication change and coprescription as a long-term therapeutic strategy. Transition from one medication to another typically takes substantially less than 9 months.

Statistical Analysis. Because our analysis included the total population of persons with schizophrenia and schizoaffective disorder, we used only descriptive statistics to explore medication use. The significance of changes from 1995 to 1999 was analyzed using Wilcoxon rank sum tests.

Results

A total of 836 persons met inclusion criteria for the full 5 study years: 599 with schizophrenia and 237 with schizoaffective disorder. The average age for participants with schizophrenia was 47.7 years (standard deviation [SD] = 14.9) and for those with schizoaffective disorder was 43.6 years (SD = 11.6). Slightly more than half (51.2%) of those with schizophrenia were males, while 46 percent with schizoaffective disorder were males. Most persons (79.2%) qualified for disability benefits because of their mental disorder.

Trends in Antipsychotic Combination Therapy. Figure 1 shows changes in psychiatric medication prescriptions for individuals with schizophrenia and schizoaffective disorder from 1995 to 1999. As shown, there were substantial decreases in the number of persons taking traditional neuroleptic antipsychotic medications and increases in those using atypical antipsychotics. By December 1999, seven in ten persons were taking an atypical antipsychotic. In addition, there were substantial increases in the prescription of antidepressants, anxiolytics, and mood stabilizers over the 5-year period.

Overall, the number of persons taking more than one antipsychotic of any type increased from 48 (5.7%) in December 1995 to 203 (24.3%) in December 1999. Simultaneous use of both traditional neuroleptics and atypical antipsychotics more than doubled from 1995 to 1999 (up 259.4%). By December 1999, almost 14 percent of all participants were taking a combination of traditional and atypical antipsychotics. Coprescription of atypical antipsychotics grew even more rapidly, resulting in 10 percent of participants taking two or more atypicals in December 1999. Among persons with schizophrenia, multiple atypical antipsychotic use increased from 9 individuals (1.5%) in 1995 to 74 (12.4%) in 1999. In the schizoaffective group, 2 (0.8%) used more than one atypical antipsychotic in 1995 compared to 19 (8%) in 1999. Coprescription of traditional medications changed little. Five persons with schizophrenia (0.8%) took two traditional neuroleptics in 1995 and in 1999. Only one person with schizoaffective disorder took two traditional medications in 1995, and none used that combination in 1999.

Combination therapy also increased for antipsychotics prescribed with psychiatric medications from other therapeutic classes. The number of persons with schizophrenia who used antidepressants increased from 111 (18.5%) in 1995 to 213 (35.6%) in 1999. SSRIs accounted for more than two-thirds of this change, increasing from 81 (13.5%) persons with coprescriptions in 1995 to 151 (25.2%) in 1999. Other novel antidepressant use grew from 12 (2.0%) persons to 41 (6.8%). The pattern was similar for individuals with schizoaffective disorder: antidepressant use increased from 48 persons (20.3%) in 1995 to 115 (48.5%) in 1999. SSRIs accounted for more than half of the increase, growing from 27 (11.4%) to 67 (28.3%). Prescriptions of other novel antidepressants increased from 10 (4.2%) to 33 (13.9%).

Anxiolytic hypnotics and mood stabilizers were used increasingly during the same period. One in five (19.9%) persons filled an anxiolytic hypnotic prescription in 1995. By December 1999, one in three (33.5%) took an anxiolytic hypnotic. Use increased by more than three-quarters (77.1%) among persons with schizophrenia and by more than half (54.1%) in persons with schizoaffective disorder.
disorder. Among all persons, the number using mood stabilizers increased from 148 (17.7%) in 1995 to 251 (30.0%) in 1999. In December 1999, 131 persons with schizophrenia (21.9%) and 120 persons with schizoaffective disorder (50.6%) filled prescriptions for mood stabilizers.

Antiparkinsonian prescriptions declined during the study period, from 241 persons in 1995 (28.8%) to 173 (20.7%) in 1999. Rates of decline were similar for schizophrenia and for schizoaffective disorder.

**Medication Treatment Intensity.** Combining psychotropic and other medications, the average person with schizophrenia or schizoaffective disorder filled prescriptions for five different medications in December 1999 (SD = 3.87), one more prescription than in 1995 and one more than did Medicaid beneficiaries without a schizophrenia-related disorder. Psychotropic medications contributed about half of this change, increasing from a mean of 2 medications in 1995 to 2.5 in 1999. Atypical antipsychotic use more than doubled (from 0.35 to 0.75 medications per person), antidepressant use increased from 0.24 to 0.37, and traditional antipsychotic use decreased from 0.53 to 0.33. These changes reflect differences in the number of people using the various drug classifications and the increased frequency of taking multiple drugs within a class.

There was a clear trend toward prescribing antipsychotic combinations for longer periods in 1999 than in 1995. The percentages of individuals taking traditional and atypical antipsychotics simultaneously for 9 or more months in a given year grew from 15.9 percent in 1995 to 27.7 percent in 1999. The number using atypical antipsychotic combinations for the same duration increased from 22.2 percent to 44.5 percent. Changes in duration were significantly different for both combinations respectively (z = 3.54, p < 0.001; z = 2.90, p = 0.004). The number of persons taking combinations of two or more traditional antipsychotics declined nonsignificantly from 56 in 1995 to 19 in 1999 (z = 0.57, p = nonsignificant).

Figure 2 shows changes in psychiatric medication costs for schizophrenia and schizoaffective disorder from 1995 to 1999. As shown, atypical antipsychotic medications accounted for the greatest growth in psychiatric medication costs. Total medication payments (including those for medications for physical disorders not shown in figure 2) increased 47.5 percent from $328 (SD = $293) per month in 1995 to $484 (SD = $373) in 1999 for persons with schizophrenia, and increased 49.3 percent from $335 (SD = $289) to $500 (SD = $339) for
those with schizoaffective disorder. One-fifth of this cost (18% and 21%) was for medications used to treat nonpsychiatric conditions, a proportion that remained stable from 1995 to 1999. The percentage of overall medication costs attributable to atypical antipsychotic medications increased from 58.7 percent to 63.8 percent among persons with schizophrenia and from 49.8 percent to 56.3 percent for those with schizoaffective disorder. Figure 3 shows the average incremental medication costs associated with various combinations of antipsychotic medications in 1999. Total drug costs for combinations of atypical antipsychotics, which represented 36.6 percent of all coprescriptions, were three to five times those of a single traditional antipsychotic. The percentage of total costs contributed by antidepressants and other psychotropic medications increased less than 1 percent.

Discussion

This analysis of prescribing trends for a cohort of Medicaid recipients with schizophrenia and schizoaffective disorder shows a clear and substantial increase in the use of combination therapy between 1995 and 1999. Remarkably, both within-therapeutic-class and across-therapeutic-class coprescription increased during the 5 study years. The greatest increase was in the practice of combining two or more antipsychotic medications, which more than quadrupled over the 5-year period. By the end of 1999, one-fourth of all persons with schizophrenia or schizoaffective disorder were taking more than one antipsychotic. Combination therapy including antipsychotics and antidepressants more than doubled during the same period, and concurrent prescriptions for anxiolytic hypnotic medications grew by more than two-thirds. Growth in the use of antipsychotics combined with mood stabilizers was similar to that of anxiolytic hypnotics. The trend toward polypharmacy as a treatment strategy was further confirmed by measures of medication treatment intensity. At the end of the study period, persons with schizophrenia or schizoaffective disorder were taking more different types of medications and were maintained on multiple antipsychotic drugs for longer periods of time. The latter suggests that our point prevalence observations did not simply capture people in the process of changing from one drug to another but reflected a trend toward long-term coprescription of antipsychotics as a therapy.
While case reports and uncontrolled clinical studies suggesting benefits of various drug combinations can be found in the literature, the evidence base for the benefits of combining two or more antipsychotics is sparse (Meltzer and Kostakoglu 2000). In contrast, combining antipsychotics with antidepressants has been proven to be effective in the treatment of comorbid depression in schizophrenia (Siris 2000). It is noteworthy that the greatest increase in antipsychotic and antidepressant combination therapy was for atypical antipsychotic agents and SSRIs. Although this combination may be selected with the goal of maximizing efficacy and minimizing side effects, it also represents a concurrent prescription of agents that are among the most expensive in the Medicaid formulary. The rapid increase in the use of this combination is likely to attract scrutiny in reviews of Medicaid pharmacy expenditures, raising questions about the indications for use of this combination in the absence of clearly documented diagnosis of co-occurring major depression.

Use of anxiolytic hypnotics and mood stabilizers is more generally accepted, particularly for persons with schizoaffective disorder. Still, we see no clear explanation for the utilization rate increases observed in this study. Unlike atypical antipsychotics and, to a lesser extent, SSRIs, anxiolytic hypnotics and mood stabilizers have been widely available for more than 10 years. Recent articles suggesting the efficacy of these agents in controlling aggressive behavior may have contributed to their increased use (Lindenmayer and Kotsaftis 2000). More frequent use of these agents in combination with antipsychotics is somewhat surprising given published evidence that atypical agents are more effective than traditional medications in controlling aggression and mood (Keck et al. 2000). Finally, the slightly declining use of antiparkinsonian drugs indicates that the switch to atypical antipsychotics may be decreasing extrapyramidal symptoms, which are a risk factor for later development of tardive dyskinesia and often associated with traditional antipsychotics.

The trend toward greater coprescription, coupled with a move to medications that are putatively more effective than older ones, suggests that physicians may be making a greater effort to augment or “fine-tune” treatment response. Availability of more new antipsychotics (two medications were introduced during the study period) with fewer side effects increases the possible combinations and may encourage both physicians and their patients to experiment with various drug combinations. However, the effectiveness, safety, and efficiency of these practices are poorly understood. Finally,
an analysis of the average incremental medication costs associated with various combinations of antipsychotic medications demonstrates that there is a substantial pharmacy cost associated with combination therapy. Improvements in functioning and decreased use of high-cost acute care services may more than compensate for this additional cost. However, research has not yet addressed the effectiveness or cost-effectiveness of this increasingly common practice.

Despite the clear trends demonstrated in this analysis, there are several caveats that should be considered in interpreting the data. First, because this study is limited to a single State, care should be taken in generalizing these findings to other areas. Although we have no reason to believe that practices in that State are any different from those in other States, we cannot conclusively say that they are not. Second, readers should note that these observations represent prescribing patterns under full insurance coverage, without pharmacy benefits management and with minimal ($0.50) or no cost sharing by beneficiaries. Prescribing patterns might differ when pharmacy benefits are managed or when beneficiaries pay out of pocket for medications. Third, our data do not allow us to identify prescribing physicians; therefore, we cannot rule out the possibility that multiple prescriptions could have been due to multiple providers. Although our data do not allow us to identify all prescribers, we know of no changes, such as extension of prescribing privileges to a new group of providers, that might have significantly changed the number of prescribing practitioners.

Implications for State Policy and Practice. The trend toward using multiple antipsychotics as well as other psychotropic medications raises many questions that are not answered by current research. Are two antipsychotics really better than one? If so, which combinations are most effective? Does combination therapy of antipsychotics with SSRIs or other antidepressants result in better functioning and symptom relief for more than one-third of all persons with schizophrenia, including those who do not have a secondary diagnosis of depression? Is the additional benefit of combination therapy worth the incremental cost for the most costly pharmaceutical combinations, such as two atypical antipsychotics or atypical antipsychotics combined with SSRIs? What are the long-term effects of coprescription?

Concerns about coprescribing are both clinical and policy oriented. The evidence base for the pharmacological efficacy and cost-effectiveness of antipsychotics is almost entirely comprised of single-agent comparisons in randomized clinical trials. For example, several studies of moderate length suggest that clozapine may be equally or more cost-effective than traditional neuroleptics for some groups (Rosenheck et al. 1998; Essock et al. 2000). Remarkably, despite a substantial literature supporting the preferential use of atypical antipsychotics other than clozapine, the collective evidence supporting superior effectiveness and cost-effectiveness of these agents compared to traditional neuroleptics is mixed (Geddes et al. 2000; Revicki 2000).

Because most drug trials focus on monotherapy rather than combination therapy, the benefit of antipsychotic combination therapy is not established. The rapid growth in the use of antipsychotic combination therapy by clinicians suggests that there is a wide gap between prescribing patterns and research knowledge. Policy makers are, understandably, skeptical about the value of using expensive medication combinations for which there is no clear scientific evidence of effectiveness. In the best case, these combinations are prescribed after careful consideration of the different pharmacological properties of the agents and adequate prior trials of appropriate single-agent therapy. In addition, the best case would dictate that the increased cost of combination therapy is accompanied by substantial benefit to consumers in improved functioning, by reduced costs of inpatient and emergency care, or both. In the worst case, the trends observed reflect prescribing based on anecdotal data and an underlying assumption that “more is better” when more intensive drug treatment could increase the risk of neurological side effects and waste scarce resources without appreciable benefit to patients.

What can State policy makers do in the absence of clear guidance from the research literature? One approach is to develop systems of care that encourage systematic, rational decision making on the part of prescribing physicians. Evidence-based guidelines or algorithms can encourage physicians to first employ appropriate alternatives to combination therapy, including changes in dosage or switches to alternative agents with proven effectiveness for treatment-refractory psychosis, such as clozapine. Before implementing a trial of combination therapy, physicians should pursue a series of trials of agents with different pharmacological properties. Education and dissemination of guidelines and algorithms alone have generally been unsuccessful in modifying physician prescribing in the absence of changes in the system of care that provides decision support, reminders, and feedback to clinicians. For example, providing practice guidelines to clinicians without additional incentives or practice change interventions does not result in significant changes in provider behavior (Grimshaw and Russell 1993; Lin et al. 1995; Oxman et al. 1995). In contrast, when guidelines are integrated into practices as part of system change interventions, improvements in quality of care and patient outcomes have been demonstrated. Effective system change interventions include interactive physician education, one-on-one academic detailing, patient education,

States can also create learning systems by encouraging a spirit of empiricism among prescribing physicians. Supporting opportunities for psychiatrists to share information gained from research or practice is one way to foster learning. Claims data, automated clinical records, or other relevant sources of information can be useful for monitoring practice patterns and identifying areas for system-wide improvement. States with outcome measurement systems such as those developed through the Mental Health Statistics Improvement Program may be able to link prescription records with individual outcome information to create naturalistic learning tools. In cases where comprehensive treatment cost data are available, they may be integrated with outcomes to offer a better understanding of, and perhaps improve, the efficiency of medication use. New analytic methodologies are needed that more effectively use observational outcome data to identify promising treatment strategies. While such efforts cannot replace rigorous peer-reviewed research and randomized clinical trials, they provide useful real-time information that can provide guidance when an evidence base has not yet been established. In the absence of more definitive information on the effectiveness and cost-effectiveness of various coprescription practices, it is inappropriate to adopt policies that restrict formularies or otherwise restrict access to new medications. Such practices can not only prevent consumers from accessing beneficial medications but also increase treatment costs in other areas (Soumerai et al. 1991; Soumerai et al. 1994).

Finally, policy makers should advocate for research studies that are aimed at evaluating the effectiveness of commonly used but unproven clinical practices, with a priority on those that are associated with significant costs. Randomized clinical trials and innovative approaches to clinical outcomes research are needed to evaluate the effectiveness and cost-effectiveness of combination therapy. In the absence of an evidence base supporting the effectiveness of antipsychotic combination therapy, pressure to contain escalating Medicaid pharmacy costs may result in measures by States to restrict reimbursement for this unproven clinical practice.

References


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