Antipsychotic Polytherapy in a State Medicaid Program from 1990 to 2001

Ryan M. Carnahan, Pharm.D., M.S. [1]; Brian C. Lund, Pharm.D., M.S [2]; Paul J. Perry, Ph.D. [3,4]; Elizabeth A. Chrischilles, Ph.D. [5]; Michael Flaum, M.D. [3]

Submitted 3/5/2007; Accepted 4/1/2007. Peer Reviewed by Two Reviewers.

[1]The University of Oklahoma College of Pharmacy, Department of Clinical and Administrative Pharmacy, Tulsa, OK. [2]Laureate Psychiatric Research Center, Tulsa, OK [3]The University of Iowa Roy J. and Lucille A. Carver College of Medicine, Department of Psychiatry, Iowa City, IA. [4]Touro University—California College of Pharmacy, Vallejo, CA. [5]The University of Iowa College of Public Health, Department of Epidemiology, Iowa City, IA

Corresponding author:

Ryan Carnahan, Pharm.D., M.S., BCPP

Assistant Professor

The University of Oklahoma College of Pharmacy

2H19 Schusterman Center, 4502 E. 41st St.

Tulsa, Oklahoma 74315-2512

ryan-carnahan@ouhsc.edu

Key words: antipsychotic agents; polypharmacy; drug therapy, combination; Medicaid; drug utilization

Conflicts of interest: No conflicts of interest were identified with regards to the authors and the contents of this manuscript.

Previous Publication:

This study was previously presented in abstract form as follows: Carnahan RM, Lund BC, Perry PJ, Chrischilles EA, Flaum M. A longitudinal study of atypical antipsychotic prescribing patterns in the Iowa Medicaid population. Presented at the American College of Clinical Pharmacy annual meeting, Dallas, TX; Oct 24-27, 2004 [Abstract No. 295E].

Acknowledgements

This work was supported by the Iowa Pharmacy Foundation. The authors would like to acknowledge the Iowa Consortium for Mental Health and the Iowa Department of Human Services for their assistance in providing access to and working with the electronic Medicaid claims data for the state of Iowa. The authors would also like to thank Tae-Ryong Park, Ph.D., for his expert assistance in preparing the Medicaid data for analysis, and Bruce Alexander, Pharm.D., for his helpful input on the project.

Abstract:

Background:

Evidence supporting the use of antipsychotic polytherapy, i.e. the concurrent use of two or more antipsychotics, is extremely limited.

Methods:

Study Design: Multi-year descriptive study

Subjects: Iowa Medicaid beneficiaries 18-64 years of age receiving prescription drug coverage from 1989 to 2001.

Primary Measures: The prevalence of antipsychotic use and antipsychotic polytherapy on January 1st of each year, stratified by the type of medication and type of polytherapy.

Results:

The proportion of antipsychotic users receiving polytherapy initially decreased, from 10.0% in 1990 to 7.5% in 1994. The prevalence of polytherapy then increased consistently, reaching its maximum at 15.4% of antipsychotic users in 2001. Atypical antipsychotic polytherapy, i.e. the concurrent use of two or more atypical antipsychotics, first appeared in 1995 and increased each year after to 5.4% of antipsychotic users, or 35% of polytherapy, in 2001. The point prevalence of antipsychotic use among Medicaid beneficiaries approximately doubled, from 3,522 users (6.4%) in 1990 to 6,810 (11.6%) in 2001, magnifying the financial implications of the increase in polytherapy.

Conclusions:

Antipsychotic polytherapy use increased substantially in this population between 1995 and 2001. As antipsychotic polytherapy becomes more common, it is vital that its safety, efficacy, and cost-effectiveness be thoroughly assessed.

Introduction:

Atypical antipsychotics have rapidly replaced conventional agents as first-line pharmacologic treatments for psychotic disorders. These drugs may represent an important advance in therapy for mental illnesses, due to a reduced risk of extrapyramidal side effects (EPS) and possible advantages in efficacy compared to conventional agents.[1] However, their high cost has placed an enormous financial burden on many health care systems and payers, including government-funded programs such as Medicaid.[1,2] While atypical antipsychotic monotherapy is expensive, the concurrent use of two or more atypical antipsychotics in the same patient is even more so. Treatment with two atypical antipsychotics may also increase the risk of adverse events, including EPS, compared to monotherapy.[1,3,4] Combining a conventional with an atypical antipsychotic is less concerning from a cost perspective, but likely increases the risk of EPS and tardive dyskinesia.[3] The conventional antipsychotic may override the atypical properties of the more expensive agent by blocking D_2 receptors more completely and at locations in the brain where such blockade is undesirable, resulting in a risk of EPS and tardive dyskinesia similar to that of the conventional agent, or even worse due to the additional blockade by the atypical.[1,3] There are also unanswered questions about the metabolic risks of combining antipsychotics. Careful consideration must be given to the impact of dose and co-prescribed medications on the adverse effects of atypical antipsychotics if the full potential of their benefits is to be recognized such that they are worth the extra monetary cost.

Conclusive evidence supporting the efficacy or safety of antipsychotic polytherapy, i.e. the use of two or more antipsychotics concurrently in the same patient, is practically non-existent.[3,5] Placebo-controlled studies of antipsychotic polytherapy have been limited to the augmentation of clozapine with conventional antipsychotics or risperidone.[6-10] Results have been inconsistent, with some studies suggesting slightly improved efficacy or worsened adverse effects and others not. Adverse effects with combination treatment in these trials have included elevated prolactin, clinically significant increases in fasting blood glucose, memory deficits, akathisia, and others.[7-10] Despite the high cost and limited supporting evidence, antipsychotic polytherapy prescribing appears to be increasing.[2,11-13] However, the extent of this increase is not well-documented. Therefore, the purpose of this study was to describe antipsychotic prescribing trends in clinical practice over time, with a focus on antipsychotic polytherapy.

Methods:

This study was approved by the University of Iowa Institutional Review Board.

Sample:

The study sample comprised all persons eligible for Iowa Medicaid prescription drug benefits during the time period from July 1989 to June 2001 (fiscal years 1990-2001). From these, individuals using antipsychotic medications on January 1st of each year were identified. Since diagnostic data were not available, those individuals who were less than 18 or greater than 64 years of age on January 1st of the given year were excluded. The intent was to minimize the inclusion of children receiving antipsychotics for non-psychotic disorders or people being treated for agitation associated with dementia. In

order to assure that all information necessary to determine active drug lists was available, patients were also required to be continuously eligible for Iowa Medicaid prescription drug benefits from August to June of the given fiscal year.

Active Drug Lists:

Active drug lists for January 1st of each year were created for all patients meeting eligibility requirements for that given year, based on a subset of previously validated criteria for creating such lists.[14] Oral drugs were considered active if a prescription had been filled before or on January 1st and also after January 1st, with a time period between fills $\leq$ 90 days. Decanoate drugs were considered active based on the same criteria, except that the acceptable time period between fills was increased to $\leq$ 150 days, as they may be dispensed less often because of the availability of multi-use vials. Active drug lists were also created in the same manner for dates 45 days before and after January 1st to determine the prevalence of persistent polytherapy.

Antipsychotic Prescribing Patterns:

The point prevalence of antipsychotic use on January 1st of each calendar year, from 1990 to 2001, was determined based upon active drug lists as described above. Conventional antipsychotics included in this analysis were as follows: chlorpromazine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, pimozide, thioridazine, thiothixene, and trifluoperazine. Atypical antipsychotics (year first marketed) available

during the years of interest and included in this analysis were as follows: clozapine (1989), olanzapine (1996), quetiapine (1997), and risperidone (1994). The number and proportion of patients with two or more antipsychotics in their active drug lists, i.e. antipsychotic polytherapy, was determined and considered the primary measure in this study. Rates of concurrent use of two or more atypical antipsychotics, i.e. atypical antipsychotic polytherapy, were also calculated. In comparison to other combinations, the use of one decanoate and one oral antipsychotic was thought to represent a unique rationale leading to polytherapy. Trends were thus examined to determine how much of the observed polytherapy was represented by this type of combination. If haloperidol or fluphenazine was prescribed in both oral and decanoate form, this combination was considered polytherapy and included in the rates that are presented.

Polytherapy was considered persistent if at least two of the antipsychotics in a patient's active drug list on January 1st of a given year were also in the active drug lists created for 45 days prior to and after January 1st. If at least two of the antipsychotics were not the same as those in the January 1st active drug list, it was considered possible that multiple cross-titrations between antipsychotics were taking place throughout the time period. To be conservative, this was not considered persistent polytherapy.

Results:

Sample:

The number of persons aged 18-64 years and continuously eligible for Medicaid drug benefits from August-May of each year ranged from 49,494 to 63,929 with no consistent

pattern of change emerging. The proportion of these individuals who were female decreased over time from 73.9% in 1990 to 65.1% in 2001. Their mean age increased slightly over time, from 34.4 years in 1990 to 37.5 years in 2001.

Among prevalent antipsychotic users meeting eligibility requirements, the mean age remained relatively stable across years (range 41.5-42.4 years), as did the gender distribution (range 49.2-53.3% female). Overall, the mean (S.D.) age was 42.1 (11.6) years and 51.1% (28,810/56,418) were female. Antipsychotic users comprised a stable proportion of this sample through 1995, though the actual number of users increased, with 3,522 users in 1990 (6.4%) and 4,210 in 1995 (6.6%). No matter how it was considered, there was a clear increase in the prevalence of antipsychotic use in the Iowa Medicaid population beginning in 1996, reaching 6,810 users (11.6%) by 2001.

Antipsychotic Utilization:

The proportion of eligible Medicaid beneficiaries receiving atypical antipsychotics, oral conventional antipsychotics, and decanoate antipsychotics in each year is presented in Figure 1. Conventional antipsychotic use was fairly stable for a number of years then declined after the introduction of risperidone, which was first available in February 1994. In 2001, 1,918 persons were users of conventional antipsychotics, compared to a peak of 3,834 persons in 1994. Atypical antipsychotic use was first observed in 1992 after the introduction of clozapine. The number of people receiving clozapine generally increased over time, though the trend was not consistent in every year. In 1992, there were 136

prevalent users of clozapine. This number reached its peak of 762 in 2001. Other atypical agents were first prevalent in the 1995 active drug lists, after risperidone was introduced. The number of atypical antipsychotic users increased every year thereafter to a peak of 4,830 users in 2001.

Antipsychotic Polytherapy:

The number of antipsychotic polytherapy recipients remained fairly stable from 1990 to 1995 (range 325-358). This began increasing noticeably in 1996, reaching 1,050 by 2001. The proportion of antipsychotic users receiving antipsychotic polytherapy showed a slightly different trend, initially decreasing from 10.0% in 1990 to a nadir of 7.5% in 1994 (Figure 2). The difference in trends reflects the increasing number of prevalent antipsychotic users over time. In 1995 the proportion began to increase, despite the increasing number of users, reaching a peak of 15.4% in 2001 (Figure 2). The number and proportion of users receiving atypical antipsychotic polytherapy increased every year after 1995, the first year in which two atypical antipsychotics were available on January 1st (clozapine, risperidone). This peaked in 2001 when 5.4% of prevalent antipsychotic users received atypical antipsychotic polytherapy. The number of persons receiving one decanoate and one oral antipsychotic did not vary dramatically or display a noticeable trend (range 115-174). However, the proportion of antipsychotic polytherapy explained by this type of combination decreased substantially as the number of persons receiving multiple antipsychotics increased over time. This peaked at 44.7% in 1992 and reached a nadir of 16.6% in 2001.

About 2% of antipsychotic users received point prevalent polytherapy that was not persistent, across all years (Figure 2). This suggests about a 2% point prevalence of cross-titration between antipsychotics. The proportion of atypical antipsychotic polytherapy that was persistent ranged from 40-80% of people receiving such combinations (Figure 2). These numbers were highly sensitive to change in the first few years of atypical antipsychotic polytherapy use because of small denominators. From 1999 to 2001, persistent atypical antipsychotic polytherapy accounted for 74-80% of atypical antipsychotic polytherapy, or about 0.6-1.1% of antipsychotic users.

Discussion

Antipsychotic use increased substantially among Iowa Medicaid beneficiaries between 1990 and 2001. The number of prevalent users on January 1st of each year nearly doubled over that time. The size of the Medicaid-eligible population did not change substantially. This increase is difficult to explain, but may reflect either a change in the characteristics of Medicaid beneficiaries or the expanding list of therapeutic uses and heavy marketing of atypical antipsychotics. A reduced risk of EPS and possibly tardive dyskinesia with atypical compared to conventional antipsychotics may have led to less reluctance to prescribe these drugs for off-label indications. These hypotheses could not be confirmed because the available Medicaid data does not include psychiatric diagnoses.

The prevalence of antipsychotic polytherapy among antipsychotic users decreased initially. One might hypothesize that some of this decrease was related to the

introduction of clozapine, which may have replaced polytherapy in some patients. By 1994, the number of clozapine users (n=406) surpassed the number receiving polytherapy (n=325). However, in spite of the decreasing prevalence from 1990 to 1994, the absolute number of people receiving polytherapy remained fairly stable during this time period. This suggests that more likely explanations for the decline in prevalence during this period are a change in beneficiary characteristics or an expanding denominator arising from increasing use of antipsychotics for indications other than primary psychotic disorders. Polytherapy has previously been found to be more common in people with primary psychotic disorders (schizophrenia, schizoaffective disorder, or other psychosis) compared to those with a primary mood disorder diagnosis (bipolar disorder, major depressive disorder).[15] However, all explanations are still speculative.

After 1994, the prevalence of polytherapy increased each year, coinciding with the introduction of atypical antipsychotics other than clozapine. Over 15% of patients were receiving two or more antipsychotics concurrently in 2001 compared to 10% in 1990. The number of people receiving antipsychotic polytherapy surpassed the number receiving clozapine in 1998 and remained more common thereafter. Atypical antipsychotic polytherapy became more common as more of these agents were introduced. By 2001 atypical antipsychotic polytherapy comprised 35% of antipsychotic polytherapy overall.

About 2% of point prevalent polytherapy was not persistent. This probably represented cross-tapering between antipsychotics. It is possible that some of the non-persistent

polytherapy represented cross-tapering between different antipsychotic polytherapy regimens. The persistence of atypical antipsychotic polytherapy was variable, but a large proportion was persistent suggesting continuous use of atypical antipsychotic combinations in many cases.

The near doubling of the number of antipsychotic users is an important complement to these rates. While the rates describe dramatic shifts in prescribing patterns within users, growth in the absolute number of individuals taking an antipsychotic underscores the growth in the population affected by these patterns. For example, even though the proportion of antipsychotic users receiving polytherapy increased by just over 50% in 11 years, this represented a near tripling in the number of people receiving polytherapy. Similarly, the number of people receiving atypical antipsychotic polytherapy in 2001 was greater than the number receiving antipsychotic polytherapy of any kind in 1990, even though polytherapy constituted 15% of all antipsychotic treatment. Also, the proportion of antipsychotic polytherapy explained by the use of one decanoate and one non-decanoate antipsychotic decreased substantially, though the number of individuals with such a medication profile did not change dramatically. As a whole, antipsychotic polytherapy became more common each year after atypical antipsychotics other than clozapine were introduced. If these patterns were affected by the increase in the number of patients suffering from psychotic disorders covered by Medicaid, one would expect that those gaining benefits would generally be less severely ill than those who already had benefits with more stringent criteria. Deinstitutionalization might explain an increase

in severely ill patients receiving outpatient benefits, but no policy changes took place in the 1990s that would have likely increased the rates of deinstitutionalization.

The combination of one decanoate and one oral antipsychotic was addressed separately in the current study because it was thought to represent a unique rationale for polytherapy. In some cases this may have represented a decanoate loading period in which oral supplementation with the same antipsychotic is used until the decanoate reaches an adequate dose, at which time the oral medication could be discontinued. This practice is clearly appropriate. Alternatively, clinicians may prescribe a combination of oral and decanoate medications when a person is intermittently compliant with oral medications. The corresponding goal is to assure that patients have at least some drug in their bodies during periods of non-compliance. This practice has been criticized in that a regimen is likely to either over-treat patients when they are compliant, or under-treat them when they are not. In contrast, a decanoate antipsychotic alone could be titrated to find the right amount of drug.[3] It is possible, however, that some patients may be unable to tolerate EPS caused by the dose of a decanoate drug required for to treat their symptoms. These patients could, in theory, benefit from a lower decanoate dose and augmentation by an atypical agent, even if they only take it intermittently. The utility of such a practice has not been systematically assessed. It ultimately poses the same concerns about the conventional agent's ability to overcome another drug's atypical properties as discussed previously. With the recent introduction of long-acting injectable risperidone, the practice of combining a conventional antipsychotic in decanoate form with an atypical agent taken by mouth may fall out of favor. Long-acting injectable risperidone may

offer improved tolerability compared to conventional agents, from the standpoint of reduced EPS, as well as the benefits of decanoates in ensuring that people receive their medication.[16]

Numerous studies have evaluated the prevalence of antipsychotic polytherapy using cross-sectional designs and a wide range of estimates have been reported.[5] Observed prevalence rates can vary substantially depending on the methodology used to determine them.[15] A single-day cross-sectional survey of currently prescribed drugs is likely to include polytherapy that is representative of a cross-taper to switch from one antipsychotic to another, as well as long-term polytherapy. If period prevalence rates are used the rate is likely to be even higher. For example, if the total number of different antipsychotics prescribed during a month is the measure, this may capture abrupt switches. This measure also increases the time period over which a switch would be detected compared to a single-day cross-sectional evaluation. Other studies that restrict the definition to long-term polytherapy reduce the detection of switch-related polytherapy. Rates reported in these studies will be lower than if a single-day survey methodology was used. In this evaluation of Iowa Medicaid data, active drugs were determined based upon observed fills of each drug before and after January 1st that were within a pre-specified time period of each other. This is limited in that it will detect some switch-related polytherapy, but the requirement for fills before and after the index date will result in a reduced rate compared to single-day survey methodology. The definition of persistent polytherapy was quite conservative in this study. Thus, the reported prevalence of persistent polytherapy should exclude cross-tapers between antipsychotics,

unless a taper was particularly long (> 92 days at a minimum). Regardless of the absolute rates observed in this study, the key finding is that the prevalence of polytherapy increased substantially over time when examined using a consistent methodology to determine rates for each year.

Though the results of this study cannot necessarily be generalized to other populations, increasing prevalence of antipsychotic polytherapy has been observed elsewhere. Clark et al conducted a longitudinal study of a cohort of 836 New Hampshire Medicaid beneficiaries with a diagnosis of schizophrenia or schizoaffective disorder.[2] Patients receiving two or more antipsychotics during the month of December of each year were considered polytherapy recipients. The prevalence of polytherapy increased from 5.7% in 1995 to 24.3% in 1999. Botts et al conducted a longitudinal evaluation of antipsychotic polytherapy in the National Ambulatory Care Survey.[12] The odds that multiple antipsychotics would be prescribed at any visit where at least one antipsychotic was prescribed increased 2.5 fold from 1993-1994 to 1999-2000. In the 1993-1994 time-period, between 2% and 3% of such visits resulted in antipsychotic polytherapy compared to over 6% in the 1999-2000 time-period (estimated from figure). This survey focuses on the ambulatory care setting, so rates were likely different than would be observed in psychiatric specialty practices that see different types of patients. Increasing rates of antipsychotic polytherapy use have also been observed in acute care settings. Centorrino et al reported on antipsychotic prescribing for 349 psychiatric inpatients that were discharged from their hospital in 1998 with an antipsychotic prescription.[2] Of these patients, 15.8% were discharged with prescriptions for more than one antipsychotic.

While they did not report comparator numbers for other years, they did note that there was an increase in the number of inpatient days on which multiple antipsychotics were prescribed. Multiple antipsychotics were prescribed during 1.7% of inpatient days in 1989, 5.7% of days in 1993, and 20.0% of days in 1998. McCue et al compared discharge prescriptions from 1995 and 2000 for patients admitted to their facility that were diagnosed with schizophrenia.[13] None of the 459 patients discharged in 1995 were prescribed multiple antipsychotics, compared to 15.9% of the 584 patients discharged in 2000. Overall, these longitudinal studies are consistent with the Iowa Medicaid data indicating a substantial increase in the prevalence of antipsychotic polytherapy after 1995.

Reasons for the increasing prevalence of antipsychotic polytherapy are unclear. Rationales leading to antipsychotic polytherapy have been thoroughly reviewed by Freudenreich and Goff.[3] One likely reason for the increase is that clinicians may feel that atypical antipsychotics comprise a group drugs with more heterogeneous mechanisms of action compared to conventional agents. Thus, they may combine them with other agents more often hoping to get an enhanced effect or a reduction in adverse effects. The aforementioned randomized, controlled trials of antipsychotic polytherapy have had mixed results and larger trials will be necessary to determine risks and benefits. In addition, all of these trials involved augmentation of clozapine with other agents. Other antipsychotic combinations commonly used in clinical practice may deserve study as well.

Policy makers are charged with allocating limited resources to provide individuals in need with health care and medications. Because resources are limited, it is the responsibility of both policy makers and prescribers to consider cost as well as evidence supporting efficacy when choosing treatments. If policy makers believe resources are being wasted, they may choose to place restrictions on what they are willing to pay for. A prime example of a policy-level intervention to control costs is from the Massachusetts Medicaid program, which now requires prior authorization if two or more atypical antipsychotics, other than clozapine, are prescribed concurrently for 60 days or more.[17] Unless prescribers are extremely judicious in their use of atypical antipsychotics, this type of regulation is likely to become more common, for better or worse.

Conclusion

The prevalence of antipsychotic polytherapy increased substantially in the Iowa Medicaid population between 1995 and 2001. Similar increases in rates of polytherapy have been observed in other studies. Many questions remain regarding the optimal use of antipsychotic medications. In practice, many people with psychotic disorders may respond inadequately to monotherapy. It is unclear whether prescribers are utilizing clozapine monotherapy before resorting to polytherapy, but this practice should be encouraged due to the superior efficacy of clozapine in treatment-refractory psychoses. It is possible that antipsychotic polytherapy could have potential to produce greater improvements than monotherapy. It is also possible that this practice is often unnecessary and wasting limited resources. If clinicians choose to use this strategy, care

must be taken to evaluate the need for multiple antipsychotics because of their cost and the possibility of adverse effects. Given the increase in the prevalence of antipsychotic polytherapy in clinical practice, it is vital that researchers systematically study this practice to assess its safety and efficacy.

References

1. Stahl SM. Antipsychotic polypharmacy: Squandering precious resources? *J Clin Psychiatry* 2002; 63:93-4.
2. Clark RE, Bartels SJ, Mellman TA, Peacock WJ. Recent trends in antipsychotic combination therapy of schizophrenia and schizoaffective disorder: implications for state mental health policy. *Schizophr Bull* 2002; 28:75-84.
3. Freudenreich O, Goff DC. Antipsychotic combination therapy in schizophrenia. A review of efficacy and risks of current combinations. *Acta Psychiatr Scand* 2002; 106:323-30.
4. Carnahan RM, Lund BC, Perry PJ, Chrischilles EA. Increased risk of extrapyramidal side effect treatment associated with atypical antipsychotic polytherapy. *Acta Psychiatr Scand* 2006; 113:135-41.
5. Stahl SM, Grady MM. A critical review of atypical antipsychotic utilization: comparing monotherapy with polypharmacy and augmentation. *Curr Med Chem* 2004; 11:313-27.
6. Potter WZ, Ko GN, Zhang LD, Yan W. Clozapine in China. A review and preview of US/PRC collaboration. *Psychopharmacology* 1989; 99:S87-S97.
7. Shiloh R, Zemishlany Z, Aizenberg D et al. Sulpiride augmentation in people with schizophrenia partially responsive to clozapine. A double-blind, placebo-controlled study. *Br J Psychiatry* 1997; 171:569-73.

8. Josiasen RC, Joseph A, Kohegyi E, et al. Clozapine augmented with risperidone in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. *Am J Psychiatry* 2005; 162:130-6.

9. Yağcıoğlu AEA, Akdede K, Turgut TI, et al. A double-blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine: efficacy and safety. *J Clin Psychiatry* 2005; 66:63-72.

10. Honer WG, Thornton AE, Chen EYH, et al. Clozapine alone versus clozapine and risperidone with refractory schizophrenia. *NEJM* 2006; 354: 472-82.

11. Centorrino F, Eakin M, Bahk W, et al. Inpatient antipsychotic drug use in 1998, 1993, and 1989. *Am J Psychiatry* 2002; 159:1932-5.

12. Botts S, Hines H, Littrell R. Antipsychotic polypharmacy in the ambulatory care setting, 1993-2000. *Psychiatr Serv* 2003; 54:1086.

13. McCue RE, Waheed R, Urcuyo L. Polypharmacy in patients with schizophrenia. *J Clin Psychiatry* 2003; 64:984-9.

14. Lund BC, Chrischilles EA, Carter BL, Ernst ME, Perry PJ. Development of a computer algorithm for defining an active drug list using an automated pharmacy database. *J Clin Epidemiol* 2003; 56:802-6.

15. Jaffe AB, Levine J. Antipsychotic medication coprescribing in a large state hospital system. *Pharmacoepidemiol Drug Saf* 2003; 12:41-8.

16. Kane JM. Strategies for improving compliance in treatment of schizophrenia by using a long-acting formulation of an antipsychotic: clinical studies. *J Clin Psychiatry* 2003; 64 (suppl 16):34-40.

17. MassHealth pharmacy program atypical antipsychotic initiative. Massachusetts Division of Medical Assistance web site. Available at: http://www.mass.gov/Eeohhs2/docs/masshealth/pharmacy/antipsychotic_initiative.pdf. Accessed March 21, 2006.

Figure 1: Prevalence of antipsychotic use among Iowa Medicaid beneficiaries, overall and by antipsychotic classification

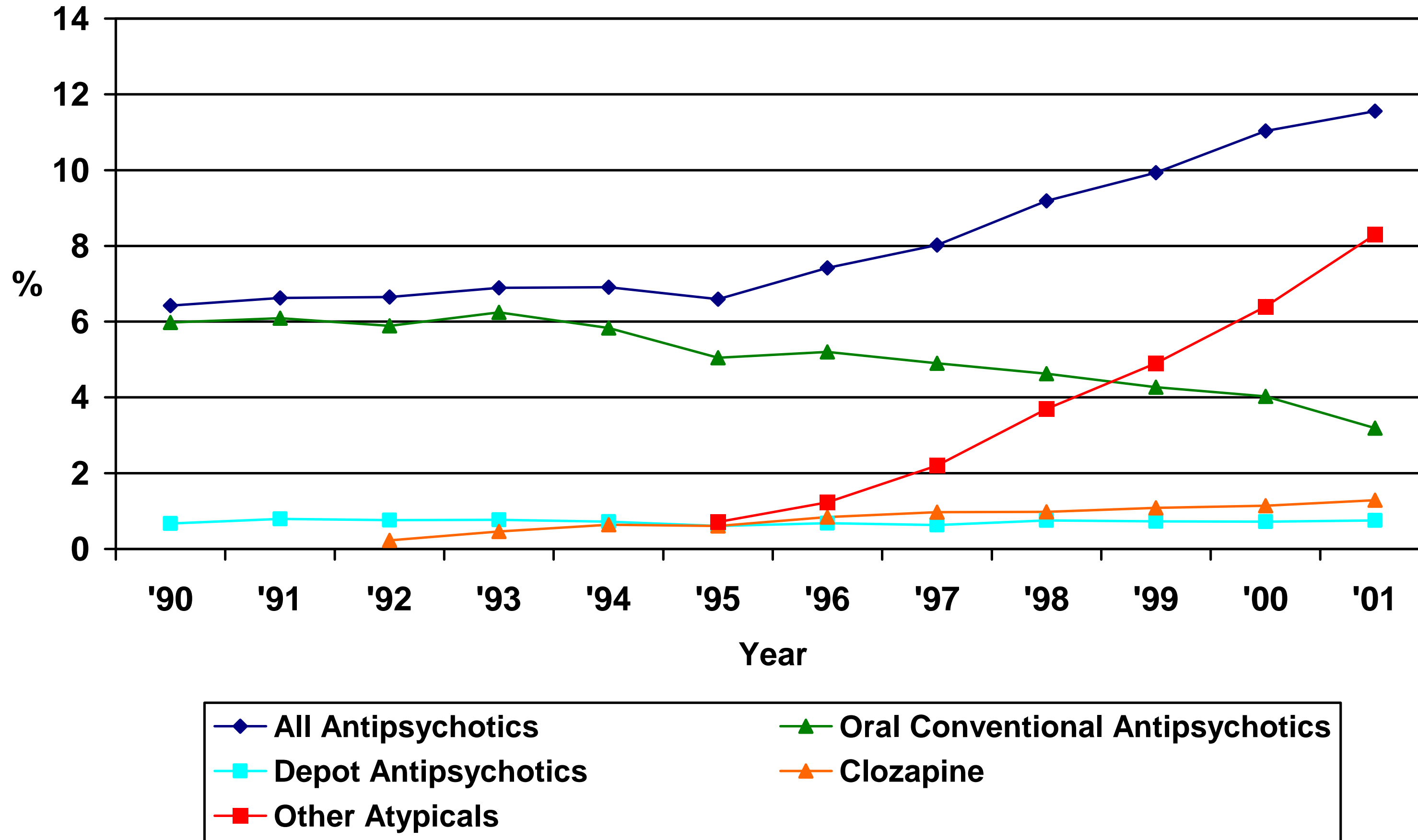

Figure 2: Diffusion of antipsychotic polytherapy among antipsychotic users, prevalence by types of combinations