

Comparison of Antipsychotic Polytherapy Use in Community and Academic Hospitals

Jessica L. Gören, PharmD, BCPP

Submitted 7/14/2008; Accepted 8/22/08. Peer reviewed by two reviewers.

Assistant Professor, University of Rhode Island, Department of Pharmacy Practice

Clinical Pharmacist Specialist, Clinical Pharmacy Department,

Cambridge Health Alliance

Instructor, Harvard Medical School, Department of Psychiatry

Corresponding author:

Jessica L. Gören, PharmD, BCPP

Clinical Pharmacist Specialist

Cambridge Health Alliance

120 Beacon Street, Suite 202

Somerville, MA 02143

Key words: antipsychotic; polypharmacy; drug combination; drug utilization

Conflicts of interest: There were no conflicts of interest with regard to this paper.

Previous Publication:

This study was previously presented in abstract form: Gören JL, Beck S, Mills B, Carlevale J, Shtasel D. Comparison of antipsychotic polypharmacy use in academic and community hospitals. Presented at the American Public Health Association annual meeting, Washington, DC; November 3-7, 2007 [Abstract No. 156476]

Abstract

Background:

Concurrent use of more than one antipsychotic (antipsychotic polytherapy) is a common practice despite evidence demonstrating increased costs and side effects with no added clinical benefit.

Methods:

Study Design: Three months descriptive study

Study sites: Academic and community hospitals within one healthcare system.

Primary outcome measure: The prevalence of antipsychotic use and antipsychotic polytherapy on adult inpatient psychiatric units located in both an academic and community hospital setting from August 1, 2005 through October 31, 2005.

Results:

The prevalence of antipsychotic polytherapy was higher in the community hospital compared with the academic hospital (39%, 28%). Concurrent use of 2, 3 and 4 antipsychotics was increased in the community hospital (25%, 13%, 1%) as compared with the academic hospital (12%, 14%, 2%). Use of two first generation or combinations of a first and second generation antipsychotic was more common in the community hospital (8.9%, 63.7%) vs. the academic hospital (6.7%, 46%), while the use of two second generation antipsychotics was more common in the academic setting (47.3%) as compared with the community setting (27.4%).

Conclusions:

The prevalence of antipsychotic polytherapy was highest in the community hospital although incidence was high in both hospital settings. The community hospital favored a less expensive form of antipsychotic polytherapy compared with the academic hospital. Given the high prevalence and lack of evidence supporting polytherapy, resources should be allocated for interventions at both community and academic facilities.

Introduction:

Rates of antipsychotic polytherapy have risen dramatically over several decades and have been reported in all treatment settings in many different countries.¹⁻⁵ In addition, rigorously controlled studies have found antipsychotic polytherapy increases side effects and cost without improving primary outcome measures. Improvements on secondary measures have been reported by a few studies. Without supporting data, the increasing rates of antipsychotic polytherapy are coming under increased scrutiny.⁶⁻⁹

Based on unique pharmacologic profiles, the combined use of a second generation antipsychotics (SGA) with another SGA or first generation antipsychotics (FGA) may represent the rational use of antipsychotic polytherapy. However, this theoretically intriguing concept is not supported by the medical literature.¹⁰⁻¹⁹ Randomized controlled clinical trials have not consistently shown antipsychotic polytherapy to be more effective than monotherapy. Of the ten randomized controlled trials, two^{13,15} reported improvement in primary outcome measures with antipsychotic polytherapy, one¹⁰ reported improvement with monotherapy, and seven found no differences between groups. Mixed results have been obtained in studies of polytherapy on secondary outcome measures, with six^{10,11,13-15,19} reporting improvements and one¹² reporting worsening of symptoms. Polytherapy exposes patients to both extrapyramidal side effects (EPS) from the FGAs and metabolic side effects associated with the SGAs.^{10-12,15,16} Use of two SGAs has been shown to increase side effects including EPS, thus eliminating one of the main advantages of SGAs.^{20,21} Multiple studies have also found increased rates of side effects such as hyperprolactinemia and sedation with a variety of antipsychotic combinations.^{10,11,15,16} In

practice, combining unique pharmacologic mechanisms of action appears to increase the side effect burden of antipsychotics without providing synergistic efficacy.

Currently, evidence is lacking due to the limited number of antipsychotic combinations reported.⁹ The trials reporting positive effects on secondary outcome measures either address augmentation of clozapine or antipsychotics medications not currently available in the US. The majority of data, positive or negative, address clozapine augmentation. However, this combination accounts for only a small percentage of antipsychotic polytherapy use.

Combinations of non-clozapine SGAs together or with FGAs are the predominate forms of antipsychotic polytherapy.^{5,21,22}

Differing definitions of polytherapy (inclusion or exclusion of as need antipsychotics, acceptable justifications, length of time of concomitant antipsychotic prescription) have hampered our ability to compare polytherapy between studies and treatment facilities. Regardless, it would be beneficial to identify areas of focus to curb prescribing of antipsychotic polytherapy. Cambridge Health Alliance represents a unique opportunity to compare rates of antipsychotic polytherapy across treatment settings due to inclusion of both academic and community hospitals. Given limited resources, we sought to identify which hospitals within the Cambridge Health Alliance were most in need of interventions to address antipsychotic polytherapy prescribing practices.

Methods:

This study was part of a quality improvement initiative and exempt from investigational review board approval.

Sample:

The study sample comprised all patients discharged on at least one antipsychotic from one of four acute adult psychiatric inpatient units between August 1, 2005 and October 31, 2005.

Data Collection:

Data were collected from the Meditech Health Care Information System used by the Cambridge Health Alliance hospitals. Computer generated data were manually reviewed to ensure all identified cases met inclusion criteria.

Antipsychotics were classified as either FGAs or SGAs. Antipsychotics included in the FGA group were as follows: chlorpromazine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, pimozide, thioridazine, thiothixene, and trifluoperazine.

Antipsychotics included in SGA group were as follows: aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone. All oral dosage forms and long acting injectable preparations were included.

Antipsychotic polytherapy was defined as concomitant use of two or more scheduled antipsychotics at discharge. Use of two forms of the same antipsychotic was not considered antipsychotic polytherapy (e.g. haloperidol oral and decanoate).

Sites:

Cambridge Health Alliance is comprised of three hospitals, more than twenty primary care and specialty practices, the Cambridge Public Health Department and the Network Health Plan. It

includes four acute adult inpatient psychiatric units, with two units housed at both the community and academic hospital. The academic hospital follows a teaching model with attending physicians, residents, interns, and students involved in patient care. The other hospital follows a traditional community model without student/trainee involvement. Both hospitals are subject to the same formulary, policies and procedures. Admission to either hospital is based solely on bed availability, making the patient populations comparable.

Antipsychotic Prescribing Patterns:

The antipsychotic prescribing patterns were determined for each hospital. Rates of concurrent use of antipsychotics were calculated. Prevalence of antipsychotic polytherapy was stratified by FGA and SGA use.

Results:

Sample:

Over the three month period 325 and 280 patients were discharged on antipsychotic agents from the community and academic hospitals, respectively. The proportion of male and female patients were similar at the community (54%, 46%) and academic (49%, 51%) hospitals. Mean age was similar between the community (36 years, range 18-64) and academic (38 years, range 18-70). Data on insurance status or ethnicity was not available.

Antipsychotic Polytherapy

Overall antipsychotic polytherapy was more common in the community hospital as compared with the academic hospital (39% vs. 28%). Specifically, use of 2, 3 and 4 antipsychotics was

more common at the community hospital (Figure 1). The type of antipsychotic polytherapy differed by site. The community hospital preferred combinations of FGA and SGAs, while the academic hospital preferred two SGAs.

Discussion:

Although physicians at the community hospital were more likely to prescribe multiple antipsychotics, the rate of polytherapy was high at both facilities. Most troubling was the number of patients prescribed three or more antipsychotics at both hospitals. There is currently no data addressing the safety or efficacy using three or more antipsychotics simultaneously.⁹ An initial recommendation is to prohibit the concurrent use of greater than two antipsychotics.

In clinical practice, state and local funds allocated to psychiatric care are limited, and the use of antipsychotic polytherapy has been shown to exponentially increase the cost of treatment.⁵

While the cost of antipsychotic use was not calculated, overall FGA combinations prescribed at the community hospital are far less expensive than the SGA combinations used at the academic hospital. However, given the potential for increased side effects with antipsychotic polytherapy, interventions to limit both practices should be implemented.

One major limitation of this study is that, while both hospitals are in the same health system and are subject to the same formulary, it is possible unique prescribing patterns exist. Additionally, it is possible adherence to policy and procedures differ between the two sites.

The second limitation of the study is each psychiatrist's individual prescribing philosophy.

Psychiatry prides itself on the unique and individualized care provided to each patient.^{23,24} This

is interesting since a qualitative review of prescribing patterns revealed the opposite. Rather than each patient receiving a unique treatment, any one prescriber was found to repeatedly utilize a limited number of medications and medication combinations. This indicates our patients are not receiving unique individualized care. The care they receive is from a standard set of individual prescriber preferences. This may partly explain why adherence to standardized treatment protocols improves patient outcomes on the whole.

Conclusions:

While specific combinations of antipsychotics may be site specific, rates of polytherapy are high regardless of practice setting. Interventions addressing use of two or more antipsychotics should be implemented at both academic and community hospitals.

References:

1. Barbui C, Nose M, Mazzi MA, et al. Persistence with polypharmacy and excessive dosing in patients with schizophrenia treated in 4 European countries. *Int Clin Psychopharmacol* 2006;21:355-362.
2. Gilmer TP, Dolder CR, Folsom DP, et al. Antipsychotic polypharmacy trends among Medicaid beneficiaries with schizophrenia in San Diego County, 1999 – 2004. *Psychiatric Serv* 2007;59(7):1007-1010.
3. Thompson A, Sullivan SA, Barley M, et al. The DEBIT trial: an intervention to reduce antipsychotic polypharmacy prescribing in adult psychiatry wards – a cluster randomized controlled trial. *Psychol Med* 2007;10:1-11.
4. Chong SA, Ravichandran N, Poon LY, et al. Reducing polypharmacy through the introduction of a treatment algorithm: Use of a treatment algorithm on the impact of polypharmacy. *Ann Acad Med Singapore* 2006;35:457-460.
5. Stahl SM, Grady MM. High-cost use of second generation antipsychotics under California's Medicaid Program. *Psychiatr Serv* 2006; 57(1):127-129.
6. Sabin JE, Daniels N. Improving psychiatric drug benefit management: I Lessons from Massachusetts. *Psychiatr Serv* 2006;57(7):949-951.
7. National Association of State Mental Health Program Directors Research Institute, Inc. (2007, March). Behavioral Healthcare Performance Measurement System™ Measures. Alexandria, VA, Available at www.nri-inc.org.
8. The Joint Commission. *Specification Manual for National Quality Measures-Hospital-Based Inpatient Psychiatric Services Test Set*. Oakbrook Terrace, IL: Joint Commission; 2007. Available at <http://www.jointcommission.org/NR/rdonlyres/16A2AAC6-D25B->

443C-9583-60CB4B04341E/0/HBIPSSpecManualpdf.zip

9. Gören JL, Parks JJ, Milton CG, et al. When is antipsychotic polypharmacy supported by research evidence? Implications for quality improvement. *Jt Comm J Qual Pat Saf.* (in press)
10. Anil-Yagcioglu A, Akdede BB, 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.
11. Freudenreich O, Henderson DC, Walsh JP, Culhane MA, Goff DC. Risperidone augmentation for schizophrenia partially responsive to clozapine: a double-blind, placebo-controlled trial. *Schiz Bull* 2007;92 (1-3):90-94.
12. Horner WG, Thornton AE, Chen EYH, et al. Clozapine alone versus clozapine and risperidone with refractory schizophrenia. *N Eng J Med* 2006;354:472-82.
13. Josiassen RC, Joseph A, Kohegyi E, et al. Clozapine augmentation with risperidone in the treatment of schizophrenia: a randomized, double blind, placebo controlled trial. *Am J Psychiatry* 2005;162:130-6.
14. Kotler M, Strous RD, Reznik I, et al. Sulpiride augmentation of olanzapine in the management of treatment-resistant chronic schizophrenia: evidence for improvement of mood symptomatology. *Int Clin Psychopharmacol* 2004;19:23-26.
15. Shiloh R, Zemishlany D, Aizenberg D, et al. Sulpiride augmentation in people with schizophrenia partially responsive to clozapine. A double blind, placebo controlled study. *Br J Psychiatr* 1997;171:569-573.
16. Potkin SG, Thyrum PT, Alva G, et al. The safety and pharmacokinetics of quetiapine when co-administered with haloperidol, risperidone or thioridazine. *J Clin Psychopharmacol*

2002;22:121-130.

17. Potter WZ, No GN, Zhang LD, et al. Clozapine in China: a review and preview of US/PCR collaboration. *Psychopharmacology* 1989;99:S87-S91.
18. Shim JC, Shin JG, Kelly DL, et al. Adjunctive treatment with a dopamine partial agonist, aripiprazole, for antipsychotic induced hyperprolactinemia: a placebo controlled trial. *Am J Psych* 2007;164(9):1404-1410.
19. Chang JS, Ahn YM, Park HJ, et al. Aripiprazole augmentation in clozapine-treated patients with refractory schizophrenia: an 8-week, randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2008;69: 720-731.
20. Carnahan RM, Lund BC, Perry PJ, et al. Increased risk of extrapyramidal side effect treatment associated with atypical antipsychotic polytherapy. *Acta Psychiatr Scand* 2006; 113:135-141.
21. Centorrino F, Goren JL, Hennen J, et al. Multiple vs. single antipsychotic agents for hospitalized psychiatric patients: Case-control study of risks versus benefits. *Am J Psychiatry* 2004; 161 (4): 700-706.
22. Centorrino F, Eakin M, Bahk WM, et al. Inpatient antipsychotic drug use in 1998, 1993, and 1989. *Am J Psychiatry* 2002; 159 (11): 1932-1935.
23. McKenzie K. Autonomy and automatons: managed care in the USA. *Psychiatric Bull* 1998;22:765-768.
24. Moran M. Psychiatrists outside managed care value autonomy in treatment decisions. *Psychiatric News* 2004;39(6):13.

Figure 1: Percent of Antipsychotic Monotherapy and Polytherapy by Hospital Setting

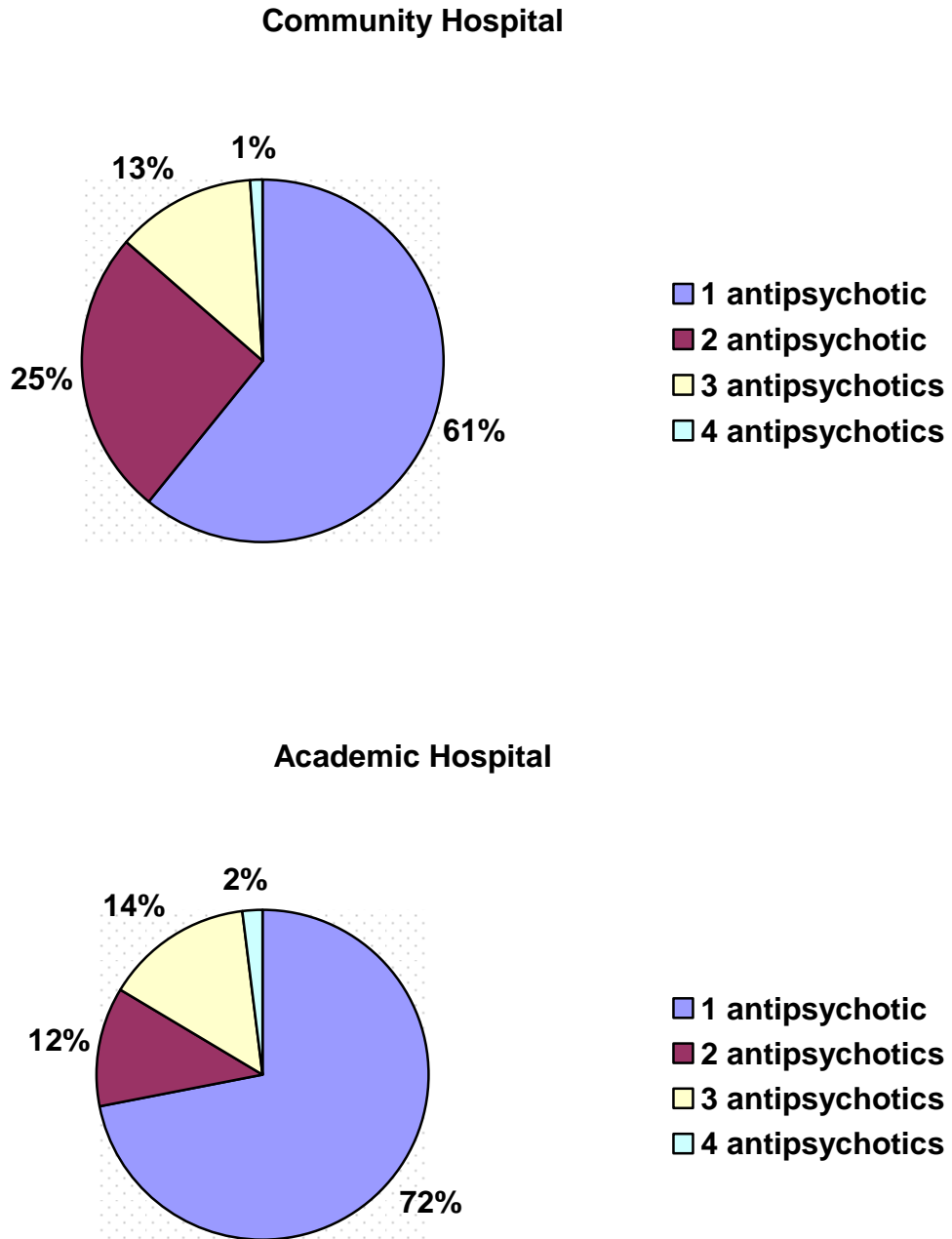


Table 1: Specific antipsychotic combinations prescribed

	Community Hospital n=325 (%)	Academic Hospital n=280 (%)
FGA + FGA	29 (8.9)	19 (6.7)
FGA + SGA	207 (63.7)	129 (46)
SGA + SGA	89 (27.4)	132 (47.3)