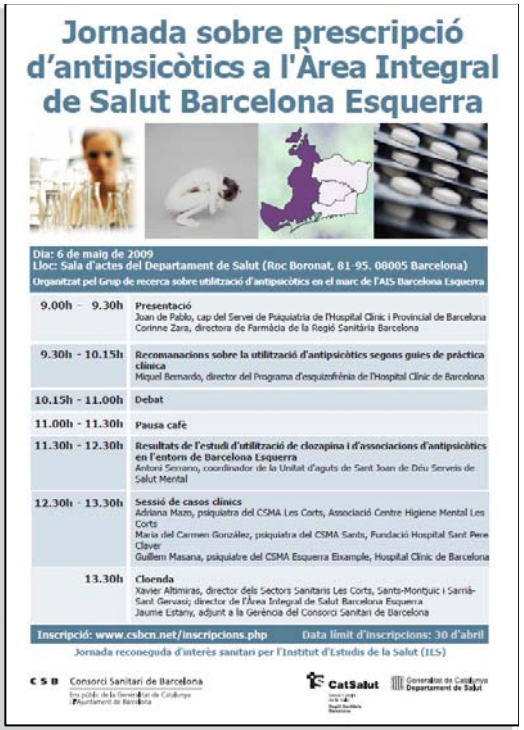
# GUIAS CLINICAS

## Jornada sobre prescripció d'antipsicòtics a l'Àrea Integral de Salut Barcelona Esquerra





### Dr. Miquel Bernardo

**Hospital Clìnic de Barcelona**
**Universitat de Barcelona**
**CIBERSAM**

# GUIAS TERAPÉUTICAS


MEDICINA CLINICA

Sábado 1 de octubre de 2005. Volumen 125 - Número 11

DOYMA

ARTÍCULO ESPECIAL

Guías terapéuticas. ¿Qué puede esperarse de ellas?

Localizador web Artículo 109.772

Alfonso Moreno-González y Grupo de Trabajo FUINSA sobre Guías Terapéuticas*

*Servicio de Farmacología Clínica. Hospital Clínico San Carlos. Madrid. España.*

- **LAS GUÍAS DE PRÁCTICA CLÍNICA SON NECESARIAS COMO CONSECUENCIA DE UN CAMBIO CONCEPTUAL Y TECNOLÓGICO QUE MODIFICA LA PRÁCTICA CLÍNICA Y COMPLICA LA TOMA DE DECISIONES**
- **CADA VEZ MÁS LOS PROFESIONALES NECESITAN JUSTIFICAR SUS DECISIONES ("ACCOUNTABILITY")**
- **ES NECESARIO DISPONER DE GUÍAS DE PRÁCTICA CLÍNICA QUE FACILITEN LA PRÁCTICA**

# www.guiasalud.es




pec Programaesquizofrènia | Clínic

Hospital Clínic de Barcelona
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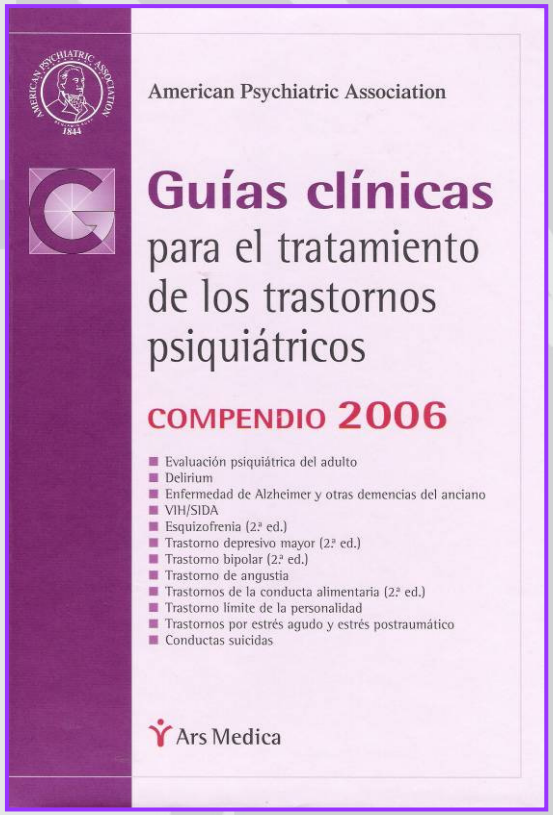
**Dr. Miquel Bernardo**

# GUÍA CLÍNICA PARA EL TRATAMIENTO DE LA ESQUIZOFRENIA 2ª Ed.




## ÍNDICE DEL CONTENIDO :

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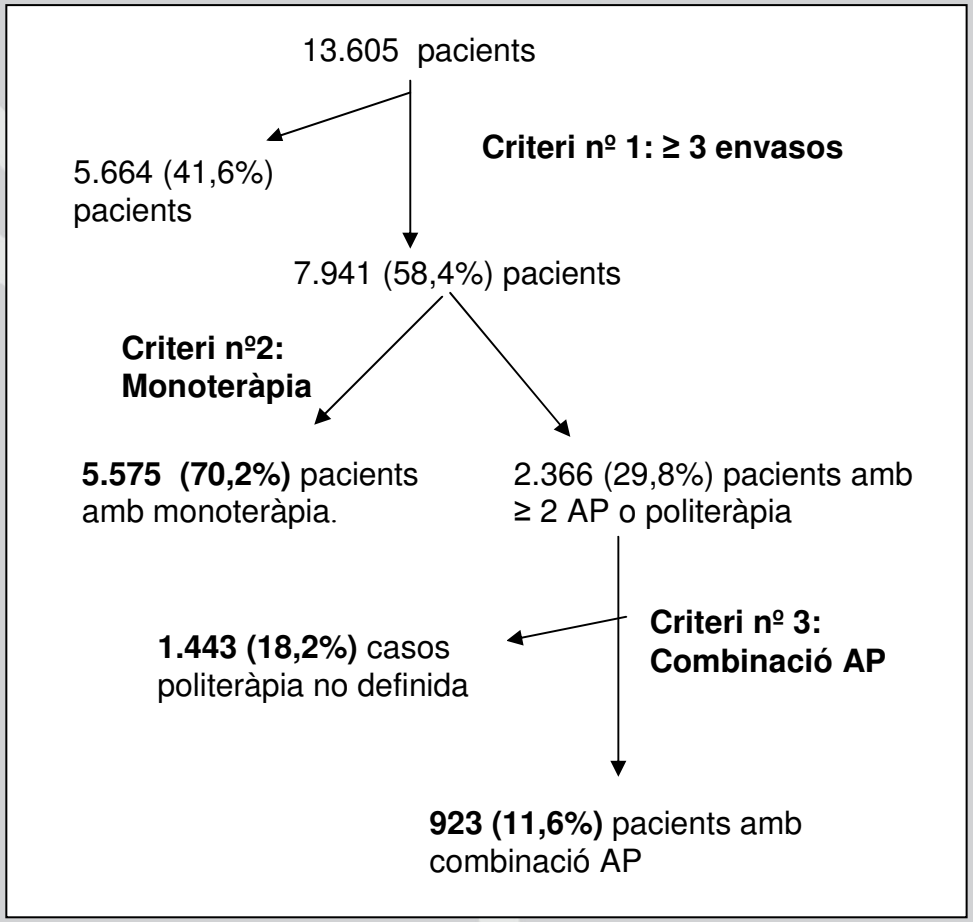
**Dr. Miquel Bernardo**

# GRUP DE RECERCA SOBRE UTILITZACIÓ D'ANTIPSICÒTICS



PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2007; **16**: 1250–1254

LETTERS TO THE EDITOR

# Antipsychotic polypharmacy at the University Psychiatric Hospital in Serbia†

The aim of the study was to analyse the prevalence of polypharmacy with antipsychotic drugs and analyse types of coprescribing episodes at the University Psychiatric Hospital in Serbia.

A sample of 120 patients (198 hospitalisations) was analysed. The prevalence of polypharmacy was calculated as the proportion of patients receiving two or more antipsychotic drugs concomitantly for at least 28 days. Total daily antipsychotic drug load was calculated as the number of defined daily doses (DDDs) of drugs per patient per day. It was compared between patients receiving monotherapy and patients receiving polypharmacy. Statistics was performed using standard statistical methods.

Monotherapy was prescribed during 32.3% hospitalisations ($n = 64$), while polypharmacy was noted in 67.7% ($n = 134$). Polypharmacy with two drugs was observed during 126 (63.6%) hospitalisations and three antipsychotics were prescribed concomitantly during 8 (4.1%) hospitalisations. Patients' characteristics were not significantly different between patients who received only monotherapy and patients receiving polypharmacy. Patients on monotherapy had significantly more prior hospitalisations than patients from the other group ($t = 3.94$, df $= 119$, $p < 0.001$).

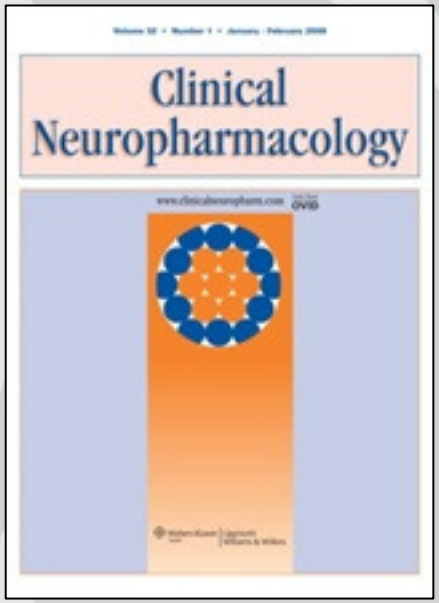
The prevalence of polypharmacy patient episodes (67.7%) is approximately 100% higher than the prevalence observed in developed European countries. The explanation of such prescribing habit of Serbian psychiatrists requires further investigation. The only distinguishing factor between patients receiving monotherapy and patients receiving polypharmacy is the number of prior hospitalisations. Copyright © 2007 John Wiley & Sons, Ltd.

*Original Article*

CLINICAL NEUROPHAR
*Volume 31, N*
*November/De*

# Antipsychotic Polypharmacy in Patients With Schizophrenia in a Brief Hospitalization Unit

*Ivan Lerma-Carrillo,* Silvia de Pablo Brühlmann,* Marta Leonor del Pozo,* Fernando Pascual-Pinazo,* Juan D. Molina, MD,* and Enrique Baca-García, MD†*




## Abstract

**Introduction:**
Antipsychotic monotherapy is considered the gold standard in pharmacological treatment of schizophrenia and other psychotic disorders. Only 2 of the main clinical guides recommend the use of antipsychotic polypharmacy (AP) for those patients refractory to monotherapy. Nonetheless, there is a large rate of studies, conducted in many different settings, showing that AP is more frequent as would be expected attending experts' recommendations.

**Methods:**
In this retrospective study, we review all the psychotropic drugs dispensed to inpatients of a brief hospitalization psychiatric unit diagnosed as having schizophrenia or schizoaffective disorder (*International Statistical Classification of Diseases, 10th Revision*) at time of discharge in the year 2005. These included a total of 209 patients older than 18 years.

**Results:**
Of the 209 studied patients, 55.5% were discharged under AP treatment. Inpatients were given a mean of 3.06 psychotropic drugs and a mean of 1.61 antipsychotics at the time of hospital discharge. A total of 33.2% of the studied patients got anticholinergic drugs, and 66.2% were given benzodiazepines. The most prevalent combination of drugs was intramuscular long-acting risperidone plus an atypical antipsychotic. Amisulpride was the most used antipsychotic as adjuvant treatment.

**Conclusions:**
Despite different clinical guidelines, AP is a common pharmacological strategy as it is shown in our study and in the reviewed literature. Data in our study indicate that the observed rates of AP cannot exclusively be attributed to the treatment of patients with clozapine-resistant schizophrenia.

Key Words: schizophrenia, antipsychotics, polypharmacy

(*Clin Neuropharmacol* 2008;31:319–332)


# Modern antipsychotic drugs: a critical overview

David M. Gardner, Ross J. Baldessarini, Paul Waraich

Abstract

CONVENTIONAL ANTIPSYCHOTIC DRUGS, used for a half century to treat a range of major psychiatric disorders, are being replaced in clinical practice by modern "atypical" antipsychotics, including aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone among others. As a class, the newer drugs have been promoted as being broadly clinically superior, but the evidence for this is problematic. In this brief critical overview, we consider the pharmacology, therapeutic effectiveness, tolerability, adverse effects and costs of individual modern agents versus older antipsychotic drugs. Because of typically minor differences between agents in clinical effectiveness and tolerability, and because of growing concerns about potential adverse long-term health consequences of some modern agents, it is reasonable to consider both older and newer drugs for clinical use, and it is important to inform patients of relative benefits, risks and costs of specific choices.

**CMAJ, 2005; 172 (13):1703-11**


# Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis

*Stefan Leucht, Caroline Corves, Dieter Arbter, Rolf R Engel, Chunbo Li, John M Davis*

## Summary

**Background** Because of the debate about whether second-generation antipsychotic drugs are better than first-generation antipsychotic drugs, we did a meta-analysis of randomised controlled trials to compare the effects of these two types of drugs in patients with schizophrenia.

**Methods** We compared nine second-generation antipsychotic drugs with first-generation drugs for overall efficacy (main outcome), positive, negative and depressive symptoms, relapse, quality of life, extrapyramidal side-effects, weight gain, and sedation.

**Findings** We included 150 double-blind, mostly short-term, studies, with 21 533 participants. We excluded open studies because they systematically favoured second-generation drugs. Four of these drugs were better than first-generation antipsychotic drugs for overall efficacy, with small to medium effect sizes (amisulpride –0·31 [95% CI –0·44 to –0·19, p<0·0001], clozapine –0·52 [–0·75 to –0·29, p<0·0001], olanzapine –0·28 [–0·38 to –0·18, p<0·0001], and risperidone –0·13 [–0·22 to –0·05, p=0·002]). The other second-generation drugs were not more efficacious than the first-generation drugs, even for negative symptoms. Therefore efficacy on negative symptoms cannot be a core component of atypicality. Second-generation antipsychotic drugs induced fewer extrapyramidal side-effects than did haloperidol (even at low doses). Only a few have been shown to induce fewer extrapyramidal side-effects than low-potency first-generation antipsychotic drugs. With the exception of aripiprazole and ziprasidone, second-generation antipsychotic drugs induced more weight gain, in various degrees, than did haloperidol but not than low-potency first-generation drugs. The second-generation drugs also differed in their sedating properties. We did not note any consistent effects of moderator variables, such as industry sponsorship, comparator dose, or prophylactic antiparkinsonian medication.

**Interpretation** Second-generation antipsychotic drugs differ in many properties and are not a homogeneous class. This meta-analysis provides data for individualised treatment based on efficacy, side-effects, and cost.

**LANCET Vol 373 January 3, 2009:3141**

# A Meta-Analysis of Head-to-Head Comparisons of Second-Generation Antipsychotics in the Treatment of Schizophrenia

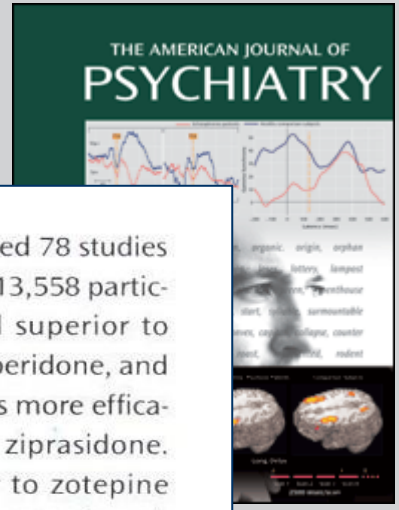
Stefan Leucht, M.D.
Katja Komossa, M.D.
Christine Rummel-Kluge,
Caroline Corves, M.Sc.
Heike Hunger
Franziska Schmid
Claudia Asenjo Lobos, M.
Sandra Schwarz
John M. Davis, M.D.

**Objective:** Whether there are differences in efficacy among second-generation antipsychotics in the treatment of schizophrenia is a matter of heated debate. The authors conducted a systematic review and meta-analysis of blinded studies comparing second-generation antipsychotics head-to-head.

**Method:** Searches of the Cochrane Schizophrenia Group's register (May 2007) and MEDLINE (September 2007) were conducted for randomized, blinded studies comparing two or more of nine second-generation antipsychotics in the treatment of schizophrenia. All data were extracted by at least three reviewers independently. The primary outcome measure was change in total score on the Positive and Negative Syndrome Scale; secondary outcome measures were positive and negative symptom subscores and rate of dropout due to inefficacy. The results were combined in a meta-analysis. Various sensitivity analyses and metaregressions were used to examine bias.

**Results:** The analysis included 78 studies with 167 relevant arms and 13,558 participants. Olanzapine proved superior to aripiprazole, quetiapine, risperidone, and ziprasidone. Risperidone was more efficacious than quetiapine and ziprasidone. Clozapine proved superior to zotepine and, in doses >400 mg/day, to risperidone. These differences were due to improvement in positive symptoms rather than negative symptoms. The results were rather robust with regard to the effects of industry sponsorship, study quality, dosages, and trial duration.

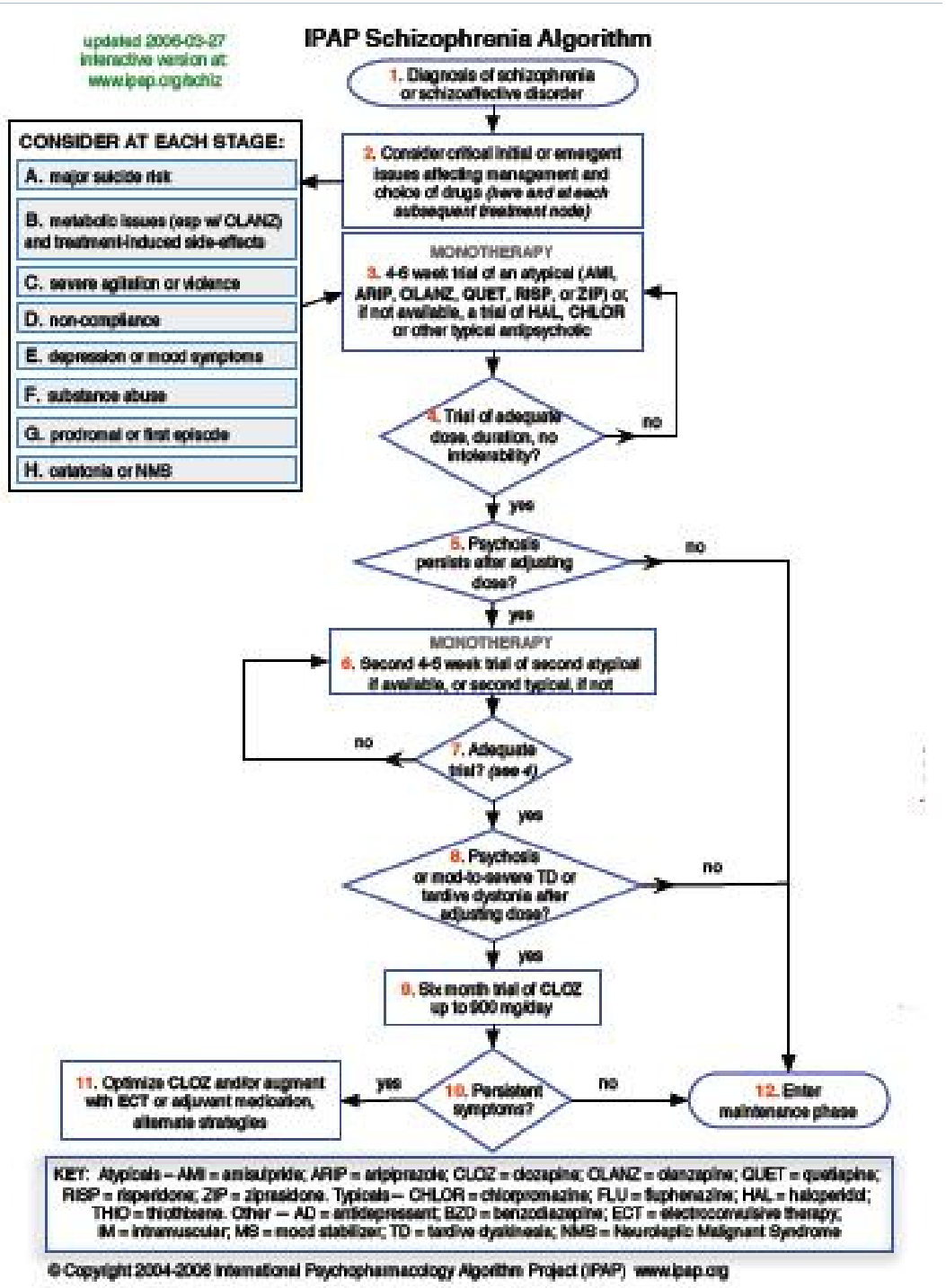
**Conclusions:** The findings suggest that some second-generation antipsychotics may be somewhat more efficacious than others, but the limitations of meta-analysis must be considered. In tailoring drug treatment to the individual patient, small efficacy superiorities must be weighed against large differences in side effects and cost.




**Am J Psychiatry. 2009 Feb; 166(2):152-63**

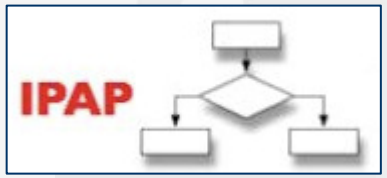
www.ipap.org

El **International Psychopharmacology Algorithm Project** (IPAP) es una organización sin ánimo de lucro establecida con el propósito de reunir a expertos en psiquiatría, la psicofarmacología, y diseño de algoritmos que permitan, mejorar y difundir el uso de algoritmos para el tratamiento sistemático de los principales trastornos psiquiátricos.



# IPAP--Schizophrenia Algorithm: Side Effects of Antipsychotics

| Item | Typical Neuroleptics | CLZ | RSP | OLZ | QTP | ZIP | ARI | AMI |
|---|---|---|---|---|---|---|---|---|
| **EPS** | some - +++ | 0 | + ( less if <4mg) | 0-+ (if <10mg) | 0 | 0 - + | 0 - + | + |
| **Tardive Dyskinesia** | ++ - +++ | 0 - rare | rare | rare | rare | rare | rare | Rare |
| **Seizures** | 0.1% - 0.3% | 2-6% | ~0.3% | ~0.9% | ~0.8% | ~0.4% | ~0.1% | Rare |
| **Sedation** | some - +++ | +++ | + | ++ | ++ | 0-++ | 0-+ | + |
| **Orthostasis** | some - +++ | +++ | ++ | + | ++ | + - ++ | + - ++ | + |
| **Cardiac,incl. QTc** | + - +++ | + - ++ | + | 0 - + | + - ++ | ++ | 0 - + | 0 - + |
| **Increased LFTs** | some - ++ | ++ | 0 - + | ++ | ++ | 0 - + | 0 - + | 0 - + |
| **Anticholinergic** | some - +++ | +++ | 0 | + | 0 - + | 0 | 0 | 0 |
| **Agranulocytosis** | ~1 in 50,000 | 6 in 1,000 | < 1 in 50,000 | < 1 in 50,000 | < 1 in 50,000 | < 1 in 50,000 | < 1 in 50,000 | < 1 in 50,000 |
| **Prolactin Elevation** | ++ - +++ | transient | +++ | + if >20mg | 0 | 0 - + | 0 | +++ |
| **Weight Gain** | some - ++ | 12 lbs. avg/10wks | 4 lbs. avg./ 6wks | 12 lbs. avg/12wks | 6 lbs. avg/6wks | 0 | 1.5 lbs. avg./6wks | 2 lbs. avg./6wks |
| **Focal Cataracts** | 0? | 0? | 0? | 0? | some risk | 0? | 0? | 0? |
| **Metabolized by CYP P450...** | various | **1A2**, 2D6, 3A4 | 2D6 | 1A2, 2D6 | 3A4 | 3A4 | 2D6, 3A4 | No |
| **Diabetes Exacerbation** | + - ++ | +++ | + | +++ | ++ | 0 | +? | 0 |
| **Hypertriglyceri-demia** | + - ++ | +++ | + | +++ | ++ | 0 | 0 | 0 |




**Dr. Miquel Bernardo**

# Antipsychotic Combinations vs Monotherapy in Schizophrenia: A Meta-analysis of Randomized Controlled Trials

Christoph U. Correll[1–4], Christine Rummel-Kluge[5], Caroline Corves, John M. Kane[2–4], and Stefan Leucht[5]

[2]The Zucker Hillside Hospital, Psychiatry Research, North Shore—Long Island Jewish Health System, Glen Oaks, New York, NY; [3]Albert Einstein College of Medicine, Bronx, New York, NY; [4]The Feinstein Institute for Medical Research, Manhasset, New York, NY; [5]Department of Psychiatry and Psychotherapy,

**Context:** Despite lacking evidence for its safety and efficacy, antipsychotic cotreatment is common in schizophrenia.

**Objective:** To evaluate therapeutic and adverse effects of antipsychotic cotreatment vs monotherapy in schizophrenia.

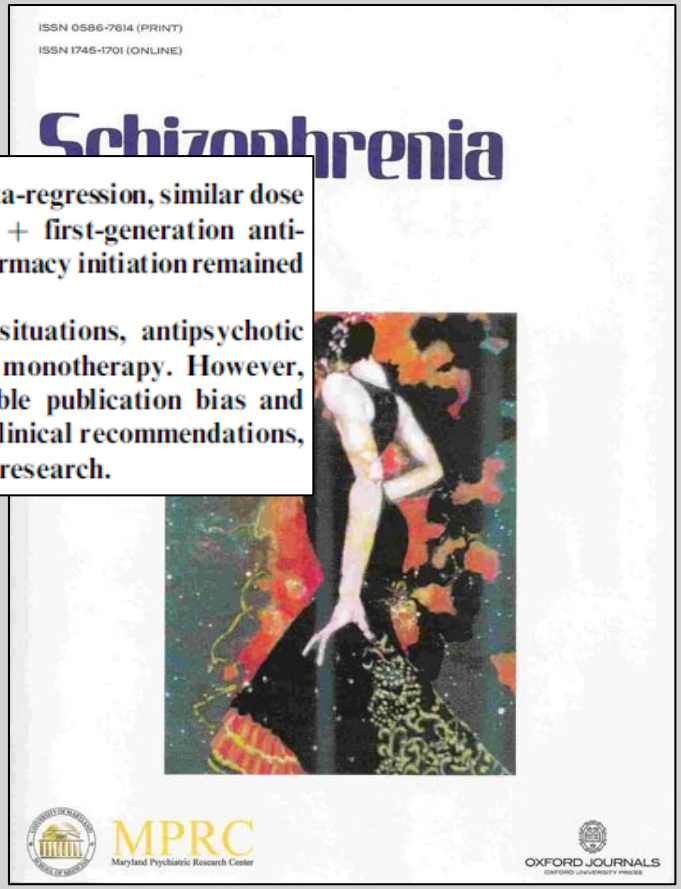
**Data Sources:** Cochrane Schizophrenia Group register and hand searches of relevant journals/conference proceedings.

**Study Selection:** Randomized controlled trials comparing antipsychotic monotherapy to cotreatment with a second antipsychotic.

**Data Extraction and Analysis:** Two authors independently extracted data. For homogenous dichotomous data, we calculated random effects, relative risk (RR), 95% confidence intervals (CIs), and numbers needed to treat (NNT). For continuous data, weighted mean differences were calculated.

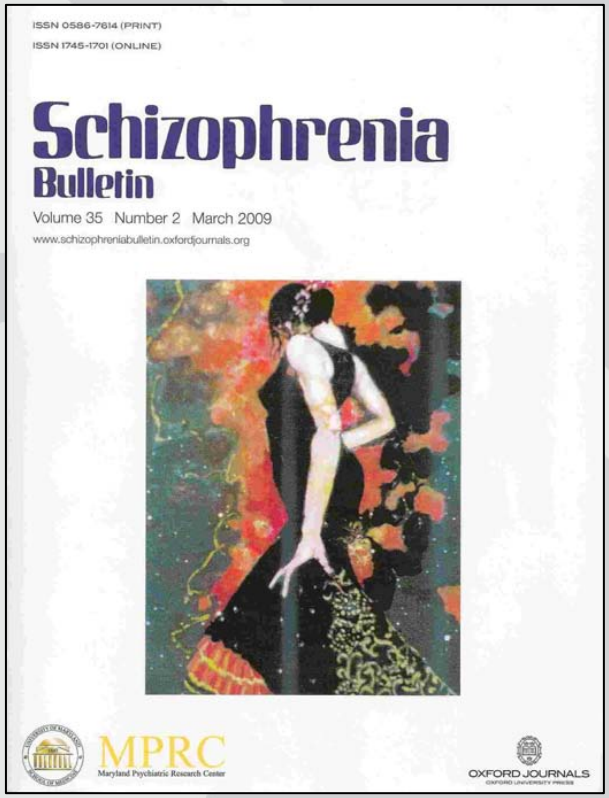
**Results:** In 19 studies (1229 patients) with 28 monotherapy and 19 cotreatment arms, antipsychotic cotreatment was superior to monotherapy regarding 2 a priori defined coprimary outcomes: less study-specific defined inefficacy ($N = 22$, $n = 1202$, RR = 0.76, CI = 0.63–0.90, $P = .002$, NNT = 7, CI = 4–17, $P = .0008$, $I^2 = 78.9\%$) and all-cause discontinuation ($N = 20$, $n = 1052$, RR = 0.65, CI = 0.54–0.78, $P < .00001$). Results were consistent using Clinical Global Impressions thresholds of less than much ($P = .006$) and less than minimally ($P = .01$) improved. Specific psychopathology and adverse event data were insufficient to yield meaningful results. In sensitivity analyses, 5 efficacy moderators emerged: concurrent polypharmacy initiation, clozapine combinations, trial duration >10 weeks, Chinese trials, and second-generation + first-generation antipsychotics. In a meta-regression, similar dose combinations, second-generation + first-generation antipsychotics and concurrent polypharmacy initiation remained significant.

**Conclusions:** In certain clinical situations, antipsychotic cotreatment may be superior to monotherapy. However, the database is subject to possible publication bias and too heterogeneous to derive firm clinical recommendations, underscoring the need for future research.




Schizophr Bull. 2009 Mar;35(2):443-57.

# Antipsychotic Combinations vs Monotherapy in Schizophrenia: A Meta-analysis of Randomized Controlled Trials




Schizophr Bull. 2009 Mar;35(2):443-57.

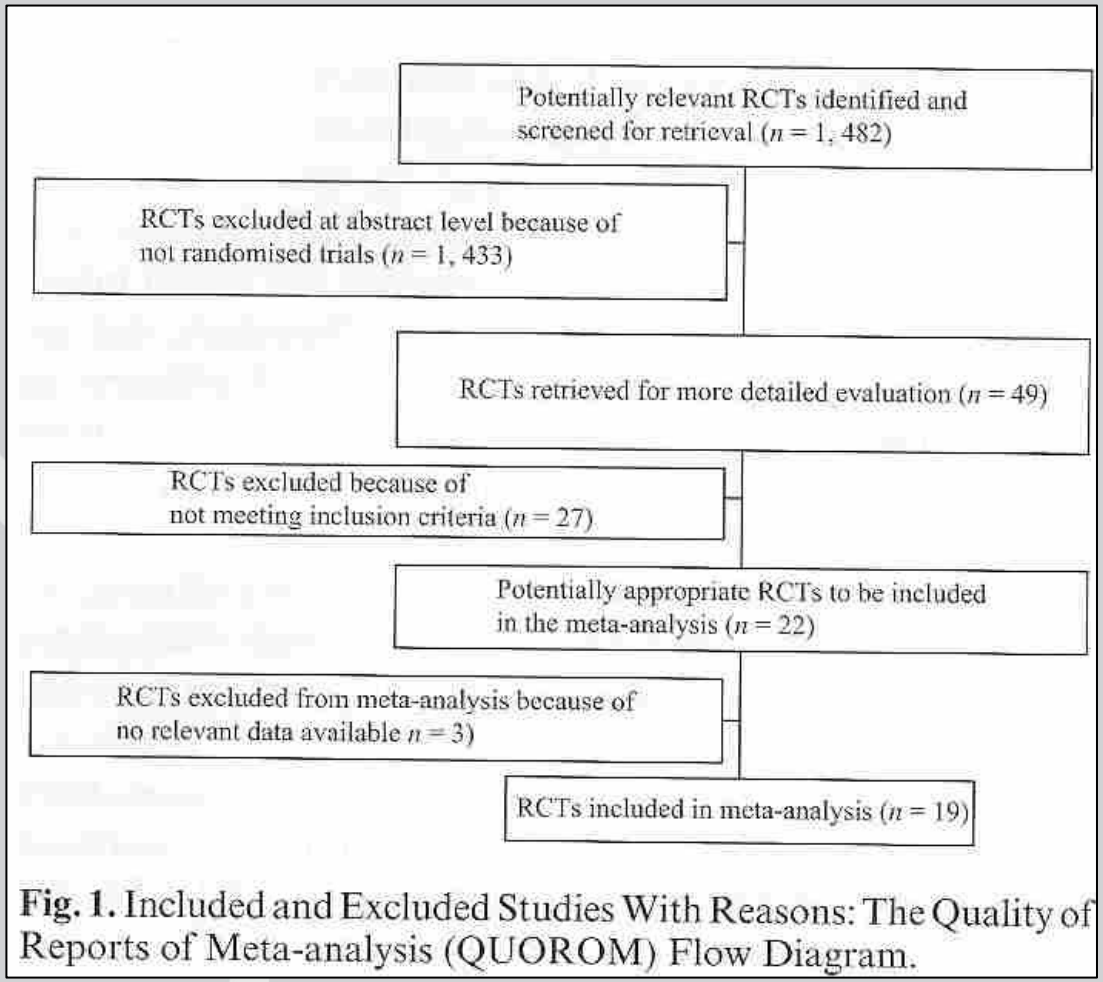



**Fig. 1.** Included and Excluded Studies With Reasons: The Quality of Reports of Meta-analysis (QUOROM) Flow Diagram.

# Proyecto Esquizofrenia PORT (Patient Outcome Research Team)

- **Objetivo**
  - Desarrollar recomendaciones basadas en la evidencia con respecto a la eficacia y la efectividad de los tratamientos para la esquizofrenia

- **Esquizofrenia PORT #1 (1992-1998)**
  - Financiado por la AHRQ (Agency for Healthcare Research and Quality) y el NIMH en 1992
  - Revisión bibliográfica (1966-1993)
  - Desarrollo de recomendaciones (publicadas en el 1998)

- **Esquizofrenia PORT #2 (2000-2002)**
  - Financiado por el NIMH Center on Services for Severe Mental Illness
  - Revisión bibliográfica (1994-2002)
  - Desarrollo de recomendaciones (publicadas en el 2004)

# Proyecto Esquizofrenia PORT (Patient Outcome Research Team)

## Esquizofrenia PORT #3 (2007-2009)

- **Investigadores y comité organizador de la conferencia**
  - Julie Kreyenbuhl, Pharm.D., Ph.D.
  - Robert W. Buchanan, M.D.
  - Lisa B. Dixon, M.D., M.P.H.
  - Faith B. Dickerson, Ph.D., M.P.H.
  - Anthony F. Lehman, M.D., M.S.P.H.

- **Objetivo**
  - Actualización de las recomendaciones basadas en la evidencia con respecto a la eficacia y la efectividad de los tratamientos para la esquizofrenia
    - · Revisión bibliográfica (2002-2008)
    - · Actualización de las recomendaciones en desarrollo

# Proyecto Esquizofrenia PORT (Patient Outcome Research Team)

## Areas de tratamiento consideradas sin suficiente evidencia para la recomendación

- Adherencia a la medicación
- Servicio al consumidor y grupos de apoyo
- Remediación cognitiva
- Esquizofrenia de inicio temprano

# Proyecto Esquizofrenia PORT (Patient Outcome Research Team)
# RECOMENDACIONES

## Polifarmacia antipsicótica

- La polifarmacia antipsicótica es un tratamiento para las personas que no han respondido adecuadamente a la monoterapia antipsicótica anterior
  - La frecuencia varia según la población
    - New York Office of Mental Health (OMH)
      - Sistema Hospitales Psiquiátricos (Jaffe and Levine, 2003) : 37%
      - Ambulatorios (datos no publicados, 2009) : 20%
    - GA and CA Medicaid recipients(Ganguly et al, 2006): 23%
    - VA National Psychosis Registry (Kreyenbuhl et al, 2006): 10%

  - Alta afinidad, los antipsicóticos de alta potencia (haloperidol, sulpirida, risperidona) puede tener algunos beneficios para los síntomas positivos residuales

# Proyecto Esquizofrenia PORT (Patient Outcome Research Team)
# RECOMENDACIONES

- **Identificar estándares fundamentales en el cuidado de la esquizofrenia**

- **Proporcionar las bases para los esfuerzos nacionales para la aplicación de prácticas basadas en pruebas**

- **Servir como indicadores de calidad para sistemas de cuidado**

- **Destacar las areas de tratamiento que necesitan más investigación**

# Recomendaciones de tratamiento de esquizofrenia PORT

## Tratamiento psicofarmacológico

| Recomendaciones de tratamiento | Tratamientos para los quales la evidencia es insuficiente para apoyar una recomendación de tratamiento |
|---|---|
| •Tratamiento antipsicótico agudo<br>•Dosis de medicación antipsicótica aguda<br>•Elección de antipsicótico para primeros episodios<br>•Dosis de medicación antipsicótica aguda para primeros episodios en esquizofrenia<br>•Mantenimiento del tratamiento con medicación antipsicótica<br>•Mantenimiento de la dosis de medicación antipsicótica<br>•Medicación antipsicótica intermitente, dirigida<br>•Estrategias de mantenimiento<br>•Mantenimiento de medicación antipsicótica de larga duración<br>•Clozapina para el tratamiento de la esquizofrenia resistente<br>•Monitorización de los niveles de clozapina en plasma<br>•Clozapina para hostilidad<br>•Clozapina para las tendencias suicidas<br>•Medicaciones antiparkinson profilácticas<br>•Estimulación magnética transcraneal repetitiva (rTMS)<br>•Medicación para el tratamioento de la agitación aguda | •Tratamiento farmacológico de los síntomas negativos<br>•Tratamiento farmacológico para mejorar cognición<br>•Elevaciones de prolactina inducidas por antipsicóticos, efectos secundarios hormonales y disfunción sexual<br>•Antipsicóticos y síndrome neuroléptico maligno (NMS)<br>•Elección de antipsicóticos y tratamiento para la discinesia tardía<br>•Antipsicóticos, calidad de vida y resultados funcionales<br>•Polifarmacia antipsicótica<br>•Tratamiento antidepresivo para la depresión<br>•Anticonvulsivos y litio para el tratamiento de los síntomas positivos resistentes<br>•Benzodiazepinas para la ansiedad, depresión o hostilidad<br>•Terapia Electroconvulsiva (TEC)<br>•Prevención farmacoológica y tratamiento del aumento de peso asociado a los antipsicótico<br>•Intervención farmacológica para el abuso de substancias y alcohol |


# Polypharmacy with Second-Generation Antipsychotics: A Review of Evidence

ANAND K. PANDURANGI, MD
ALICAN DALKILIC, MD, MPH

*Objective:* The objective of this study was to review the prevalence of polypharmacy with second-generation antipsychotics (SGAs) in clinical practice, pharmacological reasons for such practice, and the evidence for and against such polypharmacy. *Methods:* Clinical trial reports, case reports, and reviews were identified by a PubMed literature search from 1966 through October 2006, with retrieved publications queried for additional references. We excluded reports on augmentation with non-antipsychotic medications and polypharmacy involving combinations of SGAs and first-generation (conventional) antipsychotics (FGAs) or combinations of two FGAs. We identified 75 reports concerning SGA polypharmacy, from which we extracted data on study design, sample size, medications, rating scales, outcome, and conclusions. Data from randomized controlled trials and larger case series are presented in detail and case reports are briefly discussed. *Conclusions.* Polypharmacy with SGAs is not uncommon, with prevalence varying widely (3.9%–50%) depending on setting and patient population, despite limited support from blinded, randomized, controlled trials or case reports that employed an A-B-A (monotherapy-combination therapy-monotherapy) design and adequate dosing and duration of treatment. Rather than prohibiting or discouraging co-prescription of SGAs, needs of patients and clinicians should be addressed through evidence-based algorithms. Based on unmet clinical needs and modest evidence from case reports, combinations of two SGAs may merit future investigation in efficacy trials involving patients with schizophrenia who have treatment-resistant illness (including partial response) or who are responsive to treatment but develop intolerable adverse effects. Other areas that may merit future research are efficacy of SGA polypharmacy for schizophrenia accompanied by comorbid conditions (e.g., anxiety, suicidal or self-injurious behavior, aggression) and for reducing length of stay in acute care settings. (*Journal of Psychiatric Practice* 2008;14:345–367)

Journal of Psychiatric Practice 2008;14:345-367

# POLIFARMACIA CON ANTIPSICÓTICOS DE SEGUNDA GENERACION: UNA REVISION DE LA EVIDENCIA

**- ¿HAY UNA JUSTIFICACIÓN PARA LA POLIFARMACIA CON ANTIPSICÓTICOS?**

1. Para mejorar el bloqueo del receptor de dopamina ($D_2$)
2. Para lograr el antagonismo de múltiples receptores.
3. Para lograr agonismo en determinados receptores.
4. Para optimizar los efectos farmacocinéticos.
5. Para reducir los efectos adversos.
6. Durante la transición de un antipsicótico a otro.
7. Particularmente para la gestión de los síntomas objetivo.

**-¿LA POLIFARMACIA CON ASG DEMASIADO CARA?**

Modificado de Pandurangi, Journal of Psychiatric Practice 2008;14:345-367

# POLIFARMACIA CON ANTIPSICOTICOS DE SEGUNDA GENERACION: UNA REVISION DE LA EVIDENCIA

## COMBINACIONES CON CLOZAPINA

- ✓ Clozapina más Risperidona
- ✓ Clozapina más Sulpirida o Amisulprida

## OTRAS COMBINACIONES QUE INCLUYEN CLOZAPINA

- ✓ Clozapina más Olanzapina
- ✓ Clozapina más Quetiapina
- ✓ Clozapina más Ziprasidona
- ✓ Clozapina más Aripiprazol

Modificado de Pandurangi, Journal of Psychiatric Practice 2008;14:345-367

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Dr. Miquel Bernardo

# POLIFARMACIA CON ANTIPSICOTICOS DE SEGUNDA GENERACION: UNA REVISION DE LA EVIDENCIA

## COMBINACIONES DE ASG QUE NO INCLUYEN CLOZAPINA

- ✓ Risperidona más Quetiapina
- ✓ Risperidona más Ziprasidona
- ✓ Risperidona más Aripiprazola
- ✓ Risperidona más Sulpirida o Amisulprida
- ✓ Olanzapina más Quetiapina
- ✓ Olanzapina más Ziprasidona
- ✓ Olanzapina más Aripiprazola
- ✓ Olanzapina más Sulpirida o Amisulprida
- ✓ Quetiapina más Ziprasidona
- ✓ Quetiapina más Aripiprazol
- ✓ Quetiapina más Amisulprida
- ✓ Ziprasidona más Aripiprazol
- ✓ Ziprasidona más Sulpirida o Amisulprida

Modificado de Pandurangi, Journal of Psychiatric Practice 2008;14:345-367

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Schizophrenia Research 98 (2008) 323–324

# Antipsychotic polypharmacy does not increase the risk for side effects

Dear Editors,

Antipsychotic polypharmacy refers to the use of two or more antipsychotics concurrently in a single patient. Despite the lack of compelling evidence to support this treatment modality, its prevalence is as high as 50% in the inpatient setting.[1] With few theoretical benefits, it is important to examine potential shortcomings associated with this practice. One theoretical concern is the potential for an increase in adverse events which has led to the hypothesis that patients treated with a combination of two or more antipsychotics will experience a greater number of adverse events compared to patients treated with only one antipsychotic. To test the hypothesis, we examined the files of 93 inpatient that had completed UKU side effects rating scales. Sixty-one of these patients (Mean age 41.48±10.84; 70.5% Male) were treated with one antipsychotic and 32 patients (Mean age 39.47±10.03; 71.9% Male) were treated with two antipsychotics. No difference was noted between the monotherapy and polypharmacy groups respectively with regards to the proportions receiving mood stabilizers (50.8% vs. 50.0%, $p=0.94$), anticholinergics (21.3 vs. 21.9%, $p=0.95$), or benzodiazepines (24.6 vs. 34.4%, $p=0.32$). There was however a significantly greater utilization of antidepressants in the monotherapy group (40.9%) compared to the polypharmacy group (6.2%, $p<0.001$).

The UKU side effect rating scale measures spontaneously occurring adverse events over four domains (psychic, neurologic, autonomic, and other). Upon analyzing the mean number of observed adverse events across these domains, no statistically significance difference was noted between patients treated with one or two antipsychotics respectively (Psychic: 2.98±2.45 vs. 2.53±1.52, $p=0.34$; Neurologic: 1.52±1.31 vs. 1.41±1.29, $p=0.68$; Autodid not find a significant increase in the number of adverse events in patients in the polypharmacy group compared to the monotherapy group is consistent with a previous retrospective case–control study.[2] In this study, the investigators reported that the incidence of at least one adverse effect or use of an additional agent to treat adverse extrapyramidal effects was somewhat higher (but not statistically significant) among polypharmacy cases than among monotherapy comparators (40.0% vs. 25.7% respectively, $p=0.11$). However, when dosing was taken into account, the investigators found that patients (irrespective of group) with above-median chlorpromazine-equivalent doses experienced adverse effects significantly more frequently (42.6%) than those given lower doses (23.6%; relative risk=1.81; z=2.15, $p<0.04$). Unfortunately, lack of dosing information in our study precludes us from doing the same analysis. Our study is also limited in its retrospective cross sectional design, inter-rater variability, incomplete rating scales, and patient accountability. Nonetheless, this preliminary finding demonstrates the need for further studies addressing the issue of tolerability and potential risk of adverse effects associated with antipsychotic polypharmacy.

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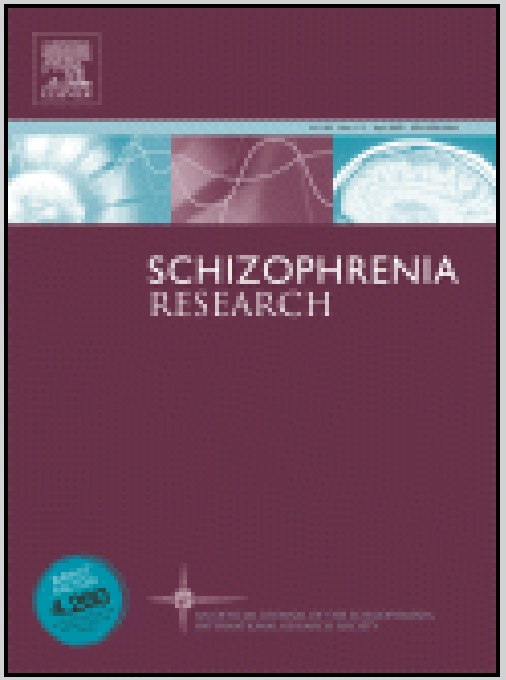
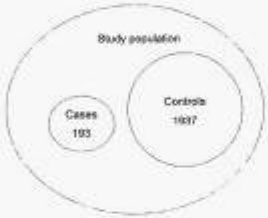


# Antipsychotic polypharmacy and risk of death from natural causes in patients with schizophrenia: a Danish nested case-control study

L Baandrup[1], C Gasse[2], VD Jensen[3], B Glenthoj[1], M Nordentoft[4], H Lublin[1], A Fink-Jensen[5], A Lindhardt[5] and PB Mortensen[2]

**Objective:** Concomitant prescription of more than one antipsychotic agent (antipsychotic polypharmacy) in the treatment of schizophrenia is prevalent although monotherapy is generally recommended. Mortality from natural causes is markedly increased in schizophrenia and the role of polypharmacy in this remains controversial. The objective was to investigate if antipsychotic polypharmacy is associated with the excess mortality from natural causes among patients with schizophrenia.

**Method:** Population-based nested case-control study using Danish central registers. From the study population of 27633 patients with schizophrenia or other mainly non-affective psychoses, aged 18-53 years, we identified 193 cases who died of natural causes within a 2-year period, and 1937 age- and sex-matched controls. Current drug use was defined as at least one prescription filled within 90 days before the date of death or the index date. The data were analysed by conditional logistic regression.




**Results:** Risk of natural death did not increase with the number of concurrently used antipsychotic agents compared with antipsychotic monotherapy (no antipsychotics: adjusted odds ratio 1.48 [95% confidence interval 0.89-2.46]; two antipsychotics: 0.91 [0.61-1.36]; three or more antipsychotics: 1.16 [0.68-2.00]). Current use of benzodiazepine derivatives with long elimination half-lives (more than 24 hours) was associated with increased risk of natural death in patients with schizophrenia treated with antipsychotics (1.78 [1.25-2.52]).

**Conclusion:** Antipsychotic polypharmacy did not contribute to the excess mortality from natural causes in middle-aged patients with schizophrenia. The detected increased risk of death associated with long-acting benzodiazepines calls for further clarification.

Odds ratio (OR) of the association between mortality from natural causes and medication

| | Crude OR (95% CI) | Adjusted OR[a] (95% CI) |
|---|---|---|
| Number of concomitant antipsychotic drugs vs. 1 (monotherapy) | | |
| 0 | 1.17 (0.74-1.87) | 1.48 (0.89-2.46) |
| 2 | 1.24 (0.86-1.77) | 0.91 (0.61-1.36) |
| ≥3 | 1.95 (1.21-3.14) | 1.16 (0.68-2.00) |
| Current use of benzodiazepine derivatives and related drugs vs. non-use | | |
| Long $T_{½}$ (more than 24 hrs) | 2.74 (2.01-3.72) | 1.78 (1.25-2.52) |
| Intermediate $T_{½}$ (6-24 hrs) | 1.02 (0.69-1.50) | 0.75 (0.49-1.15) |
| Short $T_{½}$ (less than 6 hrs) | 1.32 (0.91-1.93) | 1.16 (0.77-1.76) |

| | Crude OR (95% CI) | Adjusted OR[a] (95% CI) |
|---|---|---|
| Number of somatic co-medications vs. none | | |
| 1 | 1.34 (0.78-2.28) | 1.36 (0.79-2.34) |
| 2-4 | 1.96 (1.21-3.18) | 1.89 (1.14-3.12) |
| 5-9 | 8.21 (5.05-13.33) | 7.49 (4.47-12.54) |
| ≥10 | 28.85 (13.79-60.38) | 26.94 (12.21-59.42) |

[a]Adjusted for covariates in the final model (all antipsychotic and somatic co-medication categories, epilepsy and benzodiazepines)

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## Abstract

**Background:** This study compared the costs of antipsychotic polypharmacy for patients who initiated on 1 of the 3 most commonly prescribed atypical antipsychotics – olanzapine, quetiapine, or risperidone.

**Methods:** Data were drawn from a large, prospective, naturalistic, multi-site, nonrandomized study of treatment for schizophrenia in the United States conducted between July 1997 and September 2003. Participants who were initiated on olanzapine (N = 405), quetiapine (N = 115), or risperidone (N = 276) were followed for 1 year post initiation and compared on: (a) average daily cost of the index antipsychotic while on the index antipsychotic, (b) average daily cost of the coprescribed antipsychotics while on the index antipsychotic, (c) average daily cost of the index antipsychotic and the coprescribed antipsychotics while on the index antipsychotic, (d) total annual cost of antipsychotic medications prescribed in the year following initiation on the index antipsychotic, using propensity score-adjusted bootstrap resampling method. Average daily antipsychotic costs and total annual antipsychotic costs were also estimated using more recent (2004) antipsychotic drug prices.

**Results:** During the 1 year following initiation on the index antipsychotic, the total average daily cost of the index antipsychotic was higher for quetiapine ($15.33) than olanzapine ($13.90, $p < .05$) and risperidone ($11.04, $p < .01$), although the average daily cost of the index antipsychotic was higher for olanzapine ($10.08) than risperidone ($6.74, $p < .01$) or quetiapine ($6.63, $p < .01$). Lower total average daily costs were observed in risperidone than olanzapine or quetiapine. Significantly lower average daily cost of concomitant antipsychotic medications for olanzapine ($3.82) compared to quetiapine ($8.70, $p < .01$) or risperidone-initiated patients ($4.30, $p < .01$) contributed to the lower average daily cost of all antipsychotic medication for olanzapine-initiated patients. Each dollar spent on the index antipsychotic was accompanied by spending an additional $1.31 on concomitant antipsychotics for quetiapine compared to $0.64 for risperidone and $0.38 for olanzapine-initiated patients. A separate intent-to-treat analysis of the total annual antipsychotic cost found a significantly higher total annual antipsychotic cost for quetiapine-initiated patients ($5320) compared to olanzapine ($4536, $p < .01$) or risperidone ($3813, $p < .01$).

**Conclusion:** Prevalent antipsychotic polypharmacy adds substantial cost to the treatment of schizophrenia. Comparison of medication costs need to address the costs of all antipsychotics. A better understanding of concomitant antipsychotic costs provides a more accurate portrayal of antipsychotic medication costs in the treatment of schizophrenia.

ORIGINAL ARTICLE

# Incidence and costs of polypharmacy: data from a randomized, double-blind, pla risp pat sch

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ABSTRACT

*Objective:* The use of adjunctive psychotropics and the costs of polypharmacy in patients randomized to receive risperidone or quetiapine were compared in a placebo-controlled double-blind study conducted in India, Romania, and the United States.

*Methods:* The efficacy and safety of risperidone, quetiapine, and placebo were compared in a 14-day monotherapy phase in patients experiencing an acute exacerbation of symptoms of schizophrenia or schizoaffective disorder. This was followed by a 28-day, additive-therapy phase during which addition of antipsychotics or other psychotropic medications was permitted. Risperidone was received by 153 patients in the monotherapy phase and 133 in the additive therapy phase, quetiapine by 156 and 122, respectively, and placebo by 73 and 53. Rates of polypharmacy were examined using the Cochran–Mantel–Haenszel, Kaplan–Meier, and Cox regression methods. Costs of polypharmacy were analyzed by non-parametric Wilcoxon 2-sample tests.

*Results:* Primary study results have been reported elsewhere (Potkin *et al.*, Schizophr Res 2006;85:254-65). Mean (±SD) doses at the additive-therapy baseline were 4.7 ± 0.9 mg/day of risperidone and 579.0 ± 128.9 mg/day of quetiapine. Additional psychotropics were received by 36% of the risperidone group, 58% of the quetiapine group ($p < 0.01$), and by 58% of the placebo group. Antipsychotics accounted for > 95% of the added psychotropics, the most common being olanzapine and haloperidol. The relative risk (quetiapine vs. risperidone) for antipsychotic polypharmacy was 1.90 ($p = 0.001$; 95% CI 1.29, 2.80). The mean projected cost of additional antipsychotics per randomized patient during the additive-therapy phase was $57.03 in the risperidone group and $101.64 in the quetiapine group ($p < 0.01$).

*Conclusions:* The results confirm earlier reports of higher rates of polypharmacy with quetiapine than with risperidone. The findings also reveal substantial between-treatment differences in costs associated with polypharmacy. Limitations of the study include that the study was of short duration and that a high proportion of patients were recruited from countries other than the United States.

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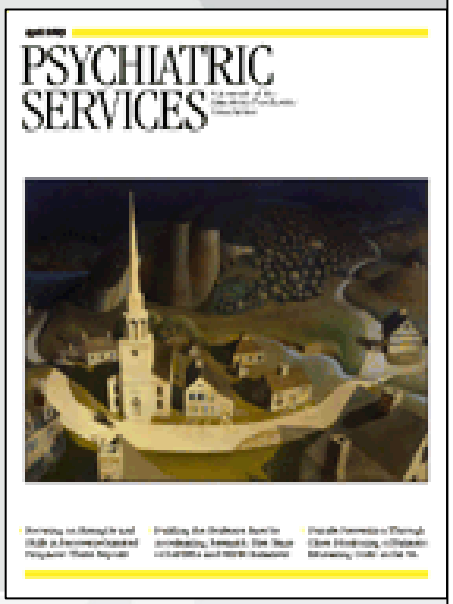


*Objective:* This study compared patients with schizophrenia whose antipsychotic medications were switched to manage treatment-resistant positive psychotic symptoms with those for whom another antipsychotic was added. Psychiatrists' characteristics and perceptions of effectiveness of the medication change on clinical outcomes were also reported. *Methods:* Psychiatrists participating in a nationally representative mailed survey (N=209) reported on the clinical features, management, and response to the change in antipsychotic medication (added versus switched) of one adult patient with treatment-refractory schizophrenia under their care for at least one year. *Results:* Thirty-three percent of patients were treated with an added antipsychotic medication. Compared with patients whose antipsychotic medications were switched, those with an added antipsychotic medication were more likely to be female, to have received care from the same psychiatrist for more than two years, and to have been recently prescribed an antidepressant. Compared with psychiatrists who switched antipsychotic prescriptions, those who added an antipsychotic reported that the change was less likely to reduce positive symptoms, improve functioning, and prevent hospitalization. Psychiatrists who added rather than switched antipsychotics reported more frequent attendance at educational programs sponsored by a pharmaceutical company. *Conclusions:* Consistent with other lines of research and practice guideline recommendations, psychiatrists perceive antipsychotic polypharmacy to be a generally ineffective strategy for treatment-resistant positive psychotic symptoms. In light of these findings, efforts to identify and implement more effective evidence-based pharmacologic approaches should be undertaken. (*Psychiatric Services* 58:983–990, 2007)

# Long-Term A
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# Characteristic

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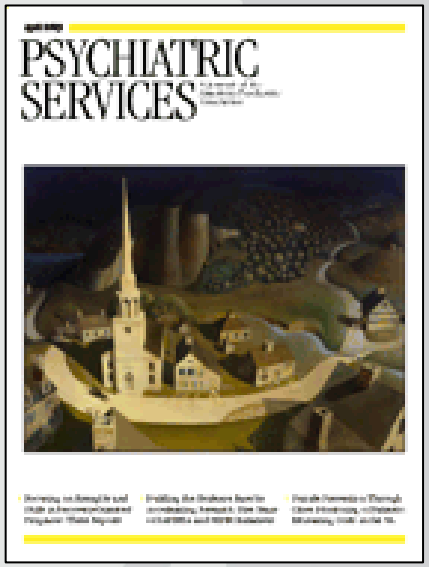


*Objective:* Although antipsychotic polypharmacy is being prescribed with increasing frequency, few studies have described patient characteristics and treatment patterns associated with long-term use of this treatment strategy. *Methods:* By using data from the National Psychosis Registry of the Department of Veterans Affairs, 5,826 patients with schizophrenia or schizoaffective disorder who received long-term antipsychotic polypharmacy (simultaneous treatment with two or more antipsychotics for 90 or more days) during fiscal year 2000 and 39,745 patients who received long-term antipsychotic monotherapy were identified. By using multivariate regression models, patient demographic and clinical characteristics, antipsychotic dosages, and use of antiparkinson and adjunctive psychotropic medications were compared between the two groups. *Results:* Patients were more likely to receive antipsychotic polypharmacy if they were younger, were unmarried, had a military service–connected disability, had schizophrenia rather than schizoaffective disorder, or had greater use of inpatient and outpatient mental health services. Patients were less likely to receive antipsychotic polypharmacy if they were African American, had concurrent diagnoses of depression or substance use disorder, or had greater medical comorbidity. For most antipsychotics, dosages prescribed for patients receiving polypharmacy were the same or modestly higher than those prescribed for patients receiving monotherapy. Patients given prescriptions for polypharmacy were more likely to receive antiparkinson medications, antianxiety agents, and mood stabilizers and equally likely to receive concurrent treatment with antidepressants. *Conclusions:* Long-term antipsychotic polypharmacy appears to be reserved for more severely ill patients with psychotic symptoms rather than mood symptoms. These patients may experience increased adverse effects as a result of excess antipsychotic exposure. (*Psychiatric Services* 58:489–495, 2007)

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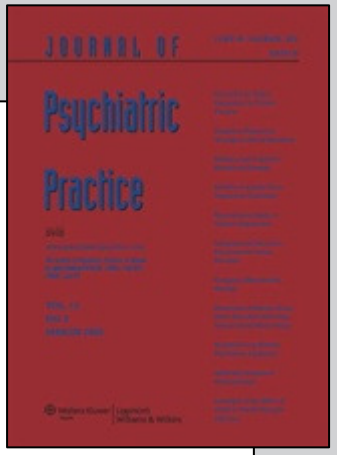
# Effectiveness of antipsychotic polypharmacy for patients with treatment refractory schizophrenia: an open-label trial of olanzapine plus risperidone for those who failed to respond to a sequential treatment with olanzapine, quetiapine and risperidone


**Objective** To evaluate the effectiveness of antipsychotic polypharmacy in a methodologically sound manner.
**Methods** In this open-label study, 17 patients with treatment-refractory schizophrenia, who failed to respond to a sequential monotherapy with olanzapine, quetiapine and risperidone, were subsequently treated with a combination therapy with olanzapine plus risperidone for at least 8 weeks.
**Results** Seven responded according to the primary endpoint defined as the post-treatment Brief Psychiatric Rating Scale being less than 70% of the pretreatment values, and they were classified as such an average of 10 weeks after the initiation of polypharmacy. Two of them were successful in a later conversion to monotherapy. None dropped out prematurely. Four (out of 13 inpatients) got better enough to be discharged from the hospital, while six patients did not show any response. The Global Assessment of Functioning score improved from 37.1 to 53.0 in responders (mean maximum dose: olanzapine 12.9 mg; risperidone 3.14 mg), while it showed non-significant changes among others (mean maximum dose: olanzapine 14.5 mg; risperidone 5.50 mg). Body weight, prolactin, and total cholesterol increased significantly.
**Conclusions** Antipsychotic polypharmacy might be sometimes helpful for difficult populations but at the cost of adverse effects. More studies of antipsychotic combination therapy versus clozapine, augmentation strategies or tenacious longer-term monotherapy are warranted for refractory schizophrenia. Copyright © 2008 John Wiley & Sons, Ltd.




# Practitioner's Corner

## When Less Is More: Reducing the Incidence of Antipsychotic Polypharmacy

WILLIAM M. TUCKER, MD

**In 2003, the New York State Office of Mental Health initiated a program aimed at supporting patient recovery by simplifying antipsychotic regimens. A key component of the program , which has been essential in supporting physician autonomy, was the introduction of a software program, Psychiatric Clinical Knowledge Enhancement System, termed "PSYCKES." This software program enables physicians to visualize at a glance the medication history of each of their patients as well as of their colleagues' patients, as a way of making better-informed decisions. The fiscal impact, in the direction of a significant reduction in antipsychotic polypharmacy, was not lost on policy-makers, who have included $1.3 million in the current state budget for the dissemination of this program.** *(Journal of Psychiatric Practice* **2007;13:202–204)**

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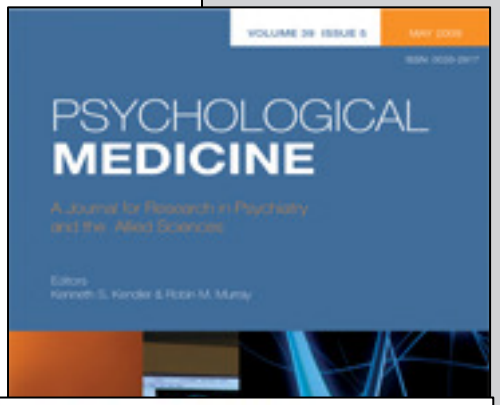
ORIGINAL ARTICLE

# The DEBIT trial: an intervention to reduce antipsychotic polypharmacy prescribing in adult psychiatry wards – a cluster randomized controlled trial




**Background.** Clinical guidelines advise against prescribing more than one antipsychotic with limited exceptions. Despite this, surveys continue to report high antipsychotic polypharmacy rates. The aim of the study was to investigate the effectiveness of a multi-faceted intervention in reducing prescribing of antipsychotic polypharmacy on general adult psychiatry wards, compared with guidelines alone.

**Method.** A pragmatic cluster randomized controlled trial recruited 19 adult psychiatric units (clusters) from the South West of England. Participants were all ward doctors and nurses. The multi-faceted intervention comprised: an educational/CBT workbook; an educational visit to consultants; and a reminder system on medication charts.

**Results.** The odds of being prescribed antipsychotic polypharmacy in those patients prescribed antipsychotic medication was significantly lower in the intervention than control group when adjusted for confounders (OR 0.43, 95% CI 0.21–0.90, $p=0.028$). There was considerable between-unit variation in polypharmacy rates and in the change in rates between baseline and follow-up (5 months after baseline).

**Conclusion.** The intervention reduced levels of polypharmacy prescribing compared to guidelines alone although the effect size was relatively modest. Further work is needed to elicit the factors that were active in changing prescribing behaviour.

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