

# Long-term outcome following early dose-reduction of antipsychotics in remitted first episode psychosis

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# Disclosure

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Research

Original Investigation

# Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy Long-term Follow-up of a 2-Year Randomized Clinical Trial

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## EDITORIAL

# Antipsychotic Medication During the Critical Period Following Remission From First-Episode Psychosis Less Is More

Patrick McGorry, MD, PhD, FRCP, FRANZCP; Mario Alvarez-Jimenez, PhD; Eoin Killackey, DPsych

*If you come to a fork in the road, take it.*  
Yogi Berra

The person recovering from a first episode of psychosis (FEP), the family, and the treating clinical team have until now faced a real dilemma. Having reached the base camp of remission of psychotic symptoms, how long should antipsychotic medication be continued? Most guidelines propose a trial of dose re-

other extreme. The former is too insensitive, but the latter might be too sensitive to serve as a basis for treatment decisions. Until now it has been assumed that relapse prevention is the top priority in treatment and a prerequisite for functional recovery, since genuine relapses are risky and distressing, setting back recovery in all domains. Although relapses were appropriately seen as a genuine threat to recovery, all too often, in research and clinical practice, prevention of relapse

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**ORIGINAL ARTICLE**

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# Long-term Antipsychotic Treatment and Brain Volumes

## A Longitudinal Study of First-Episode Schizophrenia

Beng-Choon Ho, MRCPsych; Nancy C. Andreasen, MD, PhD; Steven Ziebell, BS;  
Ronald Pierson, MS; Vincent Magnotta, PhD

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[www.neuropsychopharmacology.org](http://www.neuropsychopharmacology.org)

The Influence of Chronic Exposure to Antipsychotic Medications on Brain Size before and after Tissue Fixation: A Comparison of Haloperidol and Olanzapine in Macaque Monkeys

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It is unclear to what degree antipsychotic therapy confounds longitudinal imaging studies and post-mortem studies of subjects with schizophrenia. To investigate this problem, we developed a non-human primate model of chronic antipsychotic exposure. Three groups of six macaque monkeys each were exposed to oral haloperidol, olanzapine or sham for a 17–27 month period. The resulting plasma drug levels were comparable to those seen in subjects with schizophrenia treated with these medications. After the exposure, we observed an 8–11% reduction in mean fresh brain weights as well as left cerebrum fresh weights and volumes in both drug-treated groups compared to sham animals. The differences were observed across all major brain regions (frontal, parietal, temporal, occipital, and cerebellum), but appeared most robust in the frontal and parietal regions. Stereological analysis of the parietal region using Cavalieri's principle revealed similar volume reductions in both gray and white matter. In addition, we assessed the subsequent tissue shrinkage due to standard histological processing and found no evidence of differential shrinkage due to drug exposure. However, we observed a pronounced general shrinkage effect of ~20% and a highly significant variation in shrinkage across brain regions. In conclusion, chronic exposure of non-human primates to antipsychotics was associated with reduced brain volume. Antipsychotic medication may confound post-mortem studies and longitudinal imaging studies of subjects with schizophrenia that depend upon volumetric measures.

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**Keywords:** macaque monkeys; haloperidol; olanzapine; schizophrenia; shrinkage; stereology

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**Übersichten**

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## Frontale Hirnvolumenminderung durch Antipsychotika?

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### Review

## Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies\*



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**ORIGINAL ARTICLE**

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# Antipsychotic Drug Effects on Brain Morphology in First-Episode Psychosis

Jeffrey A. Lieberman, MD; Gary D. Tollefson, MD, PhD; Cecil Charles, PhD; Robert Zipursky, MD; Tonmoy Sharma, MD; Rene S. Kahn, MD, PhD; Richard S. E. Keefe, PhD; Alan I. Green, MD; Raquel E. Gur, MD, PhD; Joseph McEvoy, MD; Diana Perkins, MD, MPH; Robert M. Hamer, PhD; Hongbin Gu, PhD; Mauricio Tohen, MD, DrPH; for the HGDH Study Group

# A dilemma

## Article

### Relapse Duration, Treatment Intensity, and Brain Tissue Loss in Schizophrenia: A Prospective Longitudinal MRI Study

Nancy C Andreasen, M.D., Ph.D.

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Steven Ziebell, B.A.

Anvi Vora, M.D.

Beng-Choon Ho, M.D.

**Objective:** Longitudinal structural MRI studies have shown that patients with schizophrenia have progressive brain tissue loss after onset. Recurrent relapses are believed to play a role in this loss, but the relationship between relapse and structural MRI measures has not been rigorously assessed. The authors analyzed longitudinal data to examine this question.

**Methods:** The authors studied data from 202 patients drawn from the Iowa Longitudinal Study of first-episode schizophrenia for whom adequate structural MRI data were available (N=659 scans) from scans obtained at regular intervals over an average of 7 years. Because clinical follow-up data were obtained at 6-month intervals, the authors were able to compute measures of relapse number and duration and relate them to structural MRI measures. Because higher treatment intensity has been associated with smaller brain

tissue volumes, the authors also examined this countereffect in terms of dose-years.

**Results:** Relapse duration was related to significant decreases in both general (e.g., total cerebral volume) and regional (e.g., frontal) brain measures. Number of relapses was unrelated to brain measures. Significant effects were also observed for treatment intensity.

**Conclusions:** Extended periods of relapse may have a negative effect on brain integrity in schizophrenia, suggesting the importance of implementing proactive measures that may prevent relapse and improve treatment adherence. By examining the relative balance of effects, that is, relapse duration versus antipsychotic treatment intensity, this study sheds light on a troublesome dilemma that clinicians face. Relapse prevention is important, but it should be sustained using the lowest possible medication dosages that will control symptoms.

(Am J Psychiatry 2013; 170:609–615)



# Role of dopamine

- Key player in reward circuitry
- Final common pathway for psychosis
- Derangement in positive symptoms: burst activity from VTA through mesolimbic tracts
- Low VTA-(meso)frontocortical dopamine activity is associated with negative symptoms
- Dopaminergic derangement might be secondary to glutamate dysfunction (causing insufficient excitation, but also lack of inhibition in cortical areas)
- Dopaminergic blockade might be considered a peripheral therapy targeting a consequence of a derangement higher upstream

# Original discontinuation trial

## Key question

Is maintenance treatment after remission of a first episode of psychosis the best option?

# Practical issues in antipsychotic maintenance therapy

- More than 50% of patients do not accept long-term antipsychotic treatment and discontinue < 1 year
- Present guidelines do not account for differences in course characteristics or symptom profiles
- Same treatment recommendations go for remitted and nonremitted patients

*Exclusive focus on relapse prevention obscures evaluation of real-life outcome*

We did an RCT in remitted FEP comparing dose-reduction and maintenance strategy

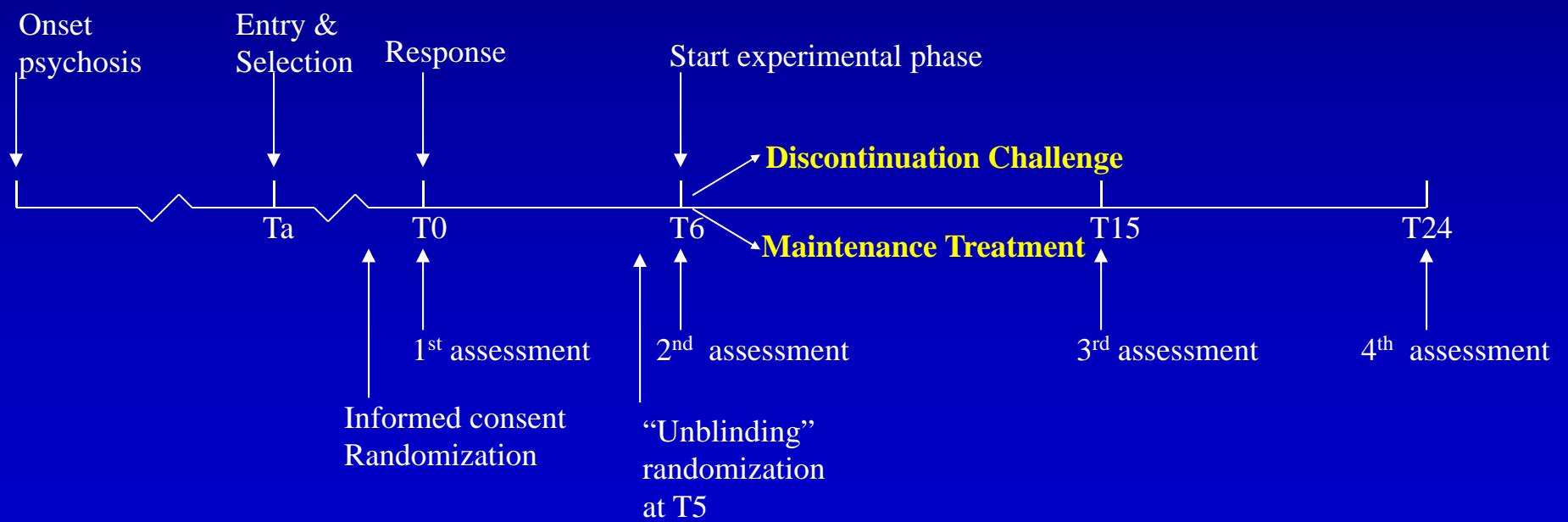
*In dose-reduction/discontinuation compared to maintenance we hypothesized:*

Better Quality of Life and Functioning levels

*Probably at the cost of:*

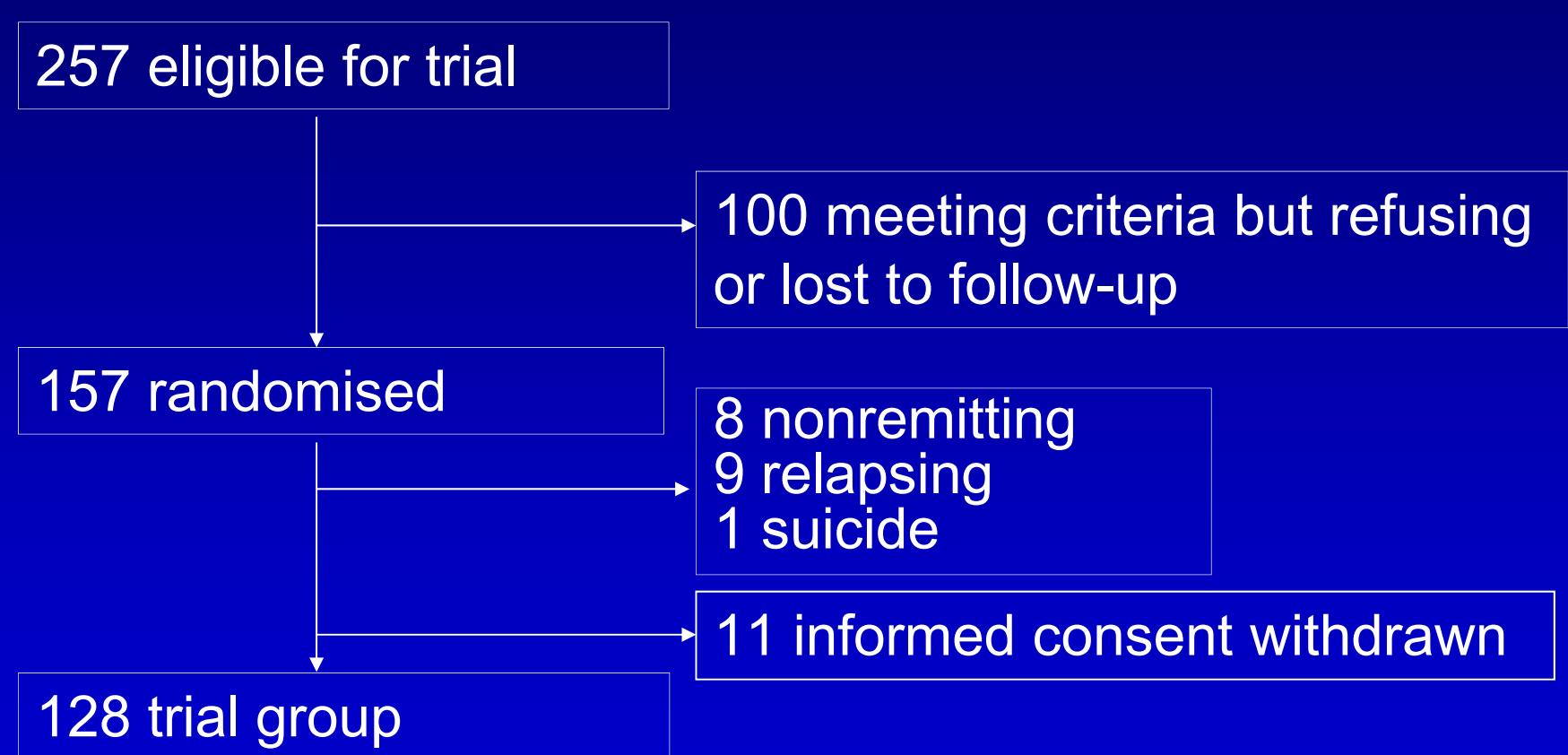
Higher relapse rates

# Design of the study



# Consort flow chart

## Oct 2001 through Dec 2002



# What we found after 2 years...

- Only 21.5% could be taken off drugs
- No difference in quality of life between arms
- No difference in functioning level, but better vocational functioning, bordering on significance  
(35% vs. 17%, OR=2.4,  $P = .06$ )
- Twice as many relapses in dose-reduction/discontinuation strategy vs. maintenance treatment: 42% against 21% in 18 months

No gains, but more relapses, though benign and relatively mild; no impact on inpatient days or symptom severity

# 7-years follow-up

- Long-term effects of dose reduction/discontinuation strategies on recovery have not been studied before
- Aim: to compare rates of recovery
- 103 (80,5%) of 128 patients were located and consented to follow-up assessment

# Participants of 7 years follow-up, n=103

- 25 non-participants: 1 suicide, 18 refused to participate, 6 lost to follow-up; no differences in baseline characteristics with participants
- No baseline differences between DR (n=52) and MT (n=51) patients in gender, DUP, age at onset, working, living alone, substance abuse, diagnosis, PANSS scores, functional capacity, quality of life

# Definitions of recovery, symptomatic and functional remission

- Recovery = meeting criteria for symptomatic and functional remission during 6 months
- Symptomatic remission: meeting working group criteria (Andreasen et al, 2005)
- Functional remission: no or only mild impairment on any of seven social functioning domains, measured by the Groningen Social Disability Scale: self-care, housekeeping, family relationships, relationships with peers, community integration, and vocational functioning

# Recovery, symptomatic and functional remission after 7 years

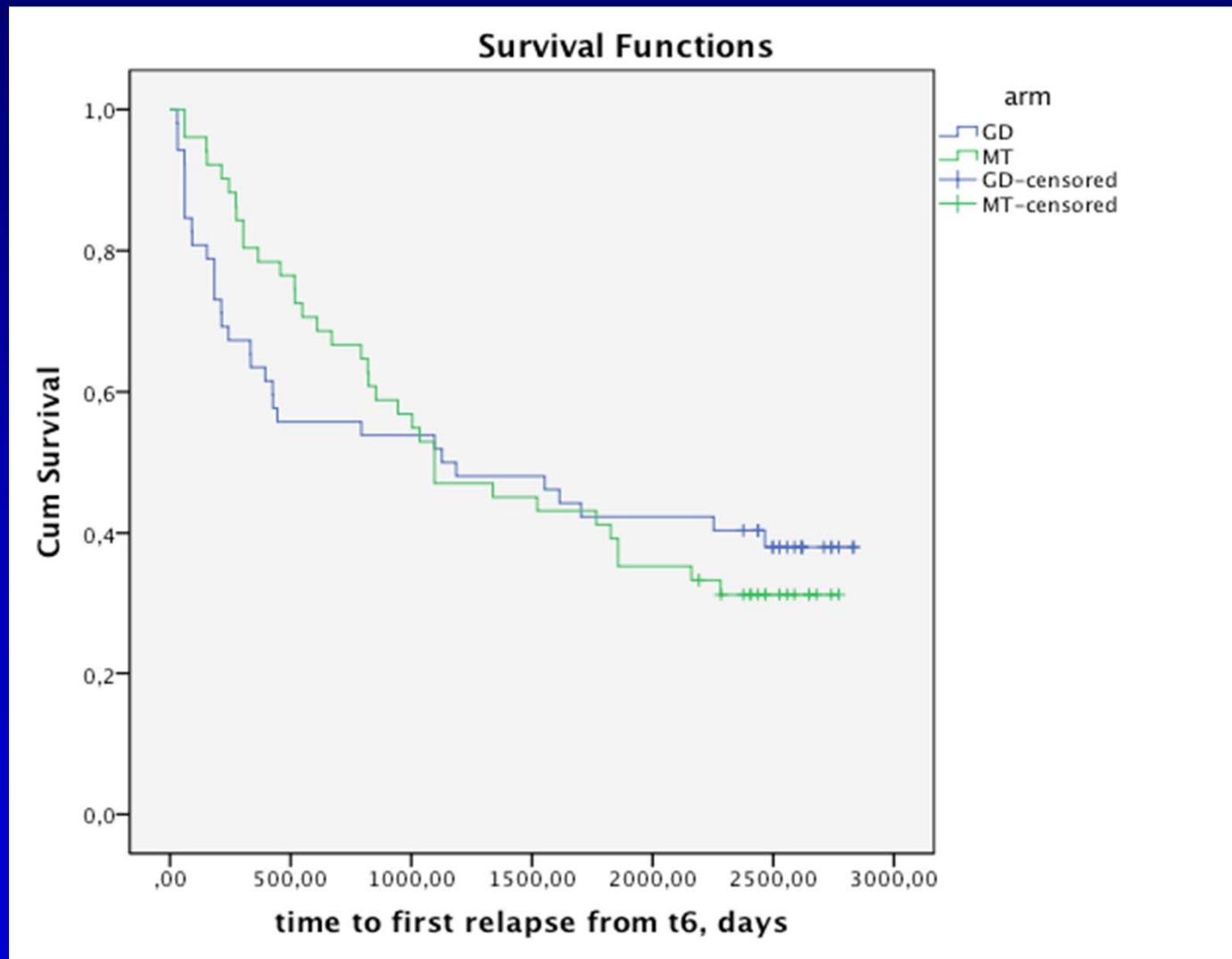
	DR (n=52)	MT (n=51)	Total sample (n=103)
Recovery	21 (40.4%)	9 (17.6%)	30 (29.1)
Symptom remission	36 (69.2%)	34 (66.7%)	70 (68.0)
Functional remission	24 (46.2%)	10 (19.6%)	34 (33.0)

# Predictors of recovery, symptomatic and functional remission, logistic regression

- n Recovery:
    - u Negative symptoms OR = .845, df = 1, P = .007
    - u Living together OR = 4.444, df = 1, P = .011
    - u Trial arm (DR) OR = 3.489, df = 1, P = .014
  - n Symptomatic remission
    - u DUP OR = .616, df = 1, P = .021
  - n Functional remission
    - u Negative symptoms OR = .852, df = 1, P = .021
    - u Living together OR = 4.682, df = 1, P = .010
    - u Social functioning OR = .857, df = 1, P = 0.40
    - u Trial arm (DR) OR = 4.617, df = 1, P = .004

# Relapse rates over 7 years of follow-up

Kaplan Meier survival analysis of time to first relapse after first remission during 7 years of follow-up in patients receiving Guided Discontinuation (GD) or Maintenance Treatment (MT) from t6 (start of trial after 6 months of first remission) to t90 (final follow-up)



# Relapse rates over 7 years of follow-up

- Relapse rates in DR and MT were not significantly different (Log Rank [Mantel-Cox]  $\chi^2=.003$ , df=1,  $P=.956$ )
- Mean number of relapses was 1.24 (SD 1.4), in DR 1.13 (SD 1.2), in MT 1.35 (SD 1.580), n.s.
- Number of patients with certain number of relapses in DR (0-5) and MT (0-8) : n.s. (Pearson  $\chi^2=4.959$ , df=6,  $P=.549$ )
- No relapse occurred in 36 (35%) of subjects

# Antipsychotic dose during the last 2 years of follow-up

- mean daily haloperidol equivalents after 7 years
  - DR: 2.20 mg (SD 2.27)
  - MT: 3.60 mg (SD 4.01)
  - Significant difference:  $t = -2.185$ ,  $P = .031$
- without patients who completely stopped antipsychotics (11 in DR and 6 in MT)
  - GD: 2.79 (SD 2.21)
  - MT: 4.08 (SD 4.03)
  - Bordering on significance:  $t = -1.813$ ,  $P = .073$

# Discontinuation and dose reduction of antipsychotics over time

	n	DR	MT
Successfully discontinued in original trial	17	14	3
Traced at 7-y follow-up	13	10	3
Restarted AP during follow-up	2	2	0
Still discontinued	11	8	3
Discontinued later on	6	3	3
Total nr. of discontinued patients	17	11	6
Nr. <1mg eq. of haloperidol	17	11	6
34 patients (33%) without substantial antipsychotic medication (42,3% in GD and 23,5% in MT)			

# Conclusions (1)

- First study to find major advantages of a dose reduction/discontinuation strategy in remitted FEP
- Recovery and functional remission rates in GD twice those of MT patients (40.4% vs. 17.6% and 46.2% vs. 19.6%)
- No difference in symptom remission rates (69.2% vs. 66.7%)
- No apparent differences in any conceivable confounders

# Conclusions (2)

- No differences on short term follow-up (2 years) but only at long-term (7 years) follow-up
- No differences in relapse rates or symptomatic domains, but only in the domains of functional capacity and recovery

*Schizophrenia treatment strategy studies should include recovery as an outcome variable, and include follow-up for more than 2 years, e.g. 5 or even 7 years.*

# Possible explanations

- Lower load of antipsychotic drugs?
  - Relief of redundant dopamine blockade, not necessary to redress psychosis
  - Better allowing cognitive and functional recovery
- Psychological impact of being able to reduce or even stop antipsychotic treatment?
  - Fitting in with current conception of doctor-patient relationship, self-management, shared decision making
  - Not a plausible explanation for large effect

# Potentially changing guidelines

- Start antipsychotics as soon as possible in active psychosis (positive symptoms above UHR threshold)
- Use the lowest effective dose, particularly in first episode psychosis (about 50% of ED90)
- In first episode patients better chances to reduce dosage
- After remission of positive symptoms try to reduce dosage as positive symptoms remain subsided, in close cooperation with the well informed patient and family members
- If possible discontinue antipsychotics, but keep on monitoring
- In case of recurrent positive symptoms restart antipsychotics or raise dosage

# MESIFOS Researchteam

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