Over de toepassing van antipsychotica bij eerste psychosen en het bevorderen van herstel

Lex Wunderink

November 26, 2015

ESPRi

Rotterdam

Disclosure

• Research Grant • Fee	• Janssen Cilag NL • Takeda

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

Lex Wunderink, MD, PhD; Roeline M. Nieboer, MA; Durk Wiersma, PhD; Sjoerd Sytema, PhD; Fokko J. Nienhuis, MA

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2013.19
Published online July 3, 2013.

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 reother 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

ORIGINAL ARTICLE

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

Übersichten

Nervenarzt 2014
DOI 10.1007/s00115-014-4027-5

V. Aderhold[1] · S. Weinmann[2] · C. Hägele[3] · A. Heinz[3]
[1] Institut für Sozialpsychiatrie, Ernst-Moritz-Arndt-Universität Greifswald, Greifswald
[2] Klinik für Psychiatrie, Psychotherapie und Psychosomatik, Vivantes Klinikum Am Urban, Berlin
[3] Klinik für Psychiatrie und Psychotherapie, Charité – Universitätsmedizin Berlin, Campus Mitte, Berlin

Frontale Hirnvolumenminderung durch Antipsychotika?

Neuropsychopharmacology (2005) 30, 1649–1661

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

Karl-Anton Dorph-Petersen[1], Joseph N Pierri[1], James M Perel[1,2], Zhuoxin Sun[3], Allan R Sampson[3] and David A Lewis*[1,4]

[1]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA; [2]Department of Clinical Pharmacology, University of Pittsburgh, Pittsburgh, PA, USA; [3]Department of Statistics, University of Pittsburgh, Pittsburgh, PA, USA; [4]Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA, USA

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.
Neuropsychopharmacology (2005) **30,** 1649–1661. doi:10.1038/sj.npp.1300710; published online 9 March 2005

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

Neuroscience and Biobehavioral Reviews 37 (2013) 1680–1691

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

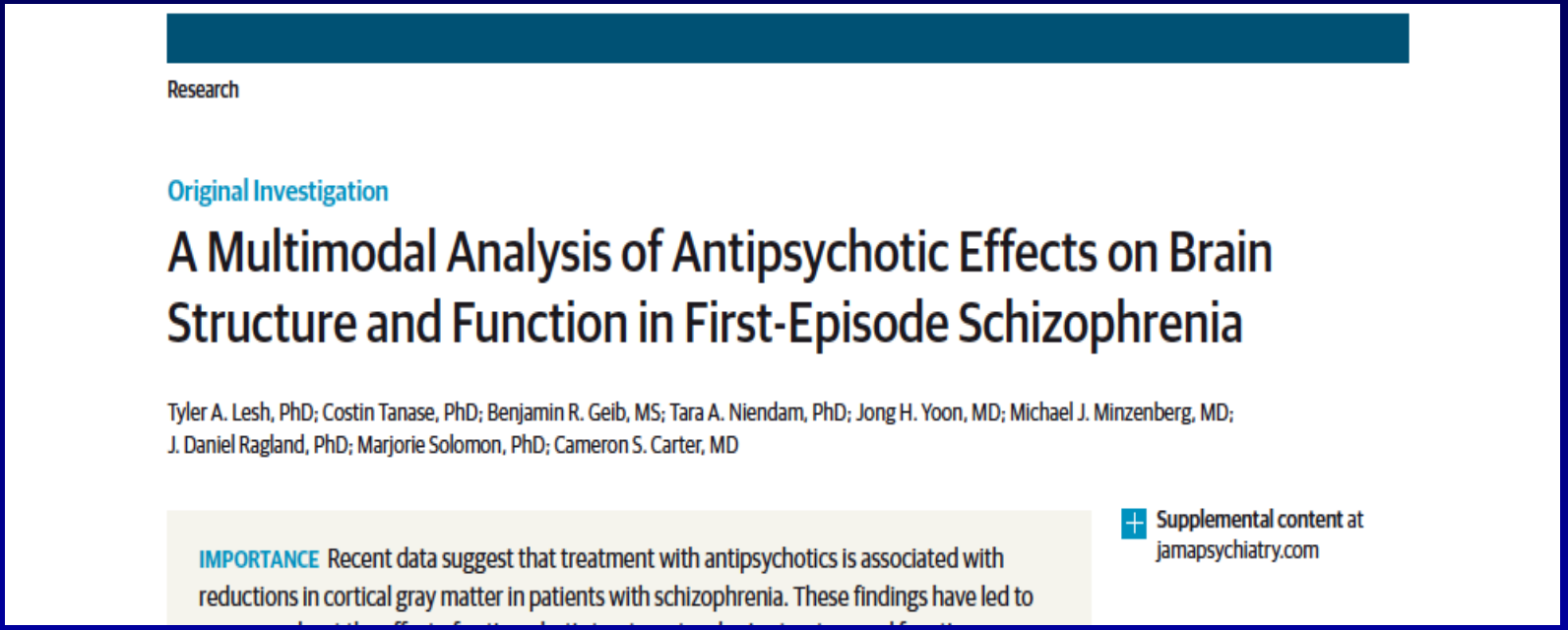
Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies☆

P. Fusar-Poli[a,*], R. Smieskova[b], M.J. Kempton[a], B.C. Ho[c], N.C. Andreasen[c], S. Borgwardt[b]

ORIGINAL ARTICLE

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



Research

Original Investigation

A Multimodal Analysis of Antipsychotic Effects on Brain Structure and Function in First-Episode Schizophrenia

Tyler A. Lesh, PhD; Costin Tanase, PhD; Benjamin R. Geib, MS; Tara A. Niendam, PhD; Jong H. Yoon, MD; Michael J. Minzenberg, MD; J. Daniel Ragland, PhD; Marjorie Solomon, PhD; Cameron S. Carter, MD

Supplemental content at jamapsychiatry.com

IMPORTANCE Recent data suggest that treatment with antipsychotics is associated with reductions in cortical gray matter in patients with schizophrenia. These findings have led to

Significant cortical thinning

- medicated patient group relative to the control group
- medicated patient group relative to the unmedicated patient group

No significant cortical thickness differences

- unmedicated patient group relative to the control group

However: better cognitive performance in medicated patients compared to unmedicated patients

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2014.2178
Published online January 14, 2015.

A true dilemma

Article

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

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

Dawei Liu, Ph.D.

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)

De rol van dopamine

- Speelt hoofdrol in het beloningscircuit en regelt drive, motivatie en nieuwsgierigheid
- Dopamine ontregeling is een van de laatste schakels in de route naar een psychose
- Ontremde dopamine burst activiteit vanuit het VTA via de mesolimbische dopamine banen veroorzaakt *hyper-salience* wat leidt tot positieve symptomen
- Maar lage dopamine activiteit in de dopamine banen van het VTA naar de frontale hersenschors gaat gepaard met verminderde drive en negatieve symptomen

Dopamine en psychose

- Dopaminerge ontregeling kan het gevolg zijn van ontregeling van de excitatie/inhibitie balans in de hersenschors, die door een meer primaire stoornis wordt veroorzaakt
- Dopaminerge blokkade kan je zien als een symptomatische behandeling van een gevolg van een hogerop gelegen stoornis

Hypothese: je hebt dopamineblokkade nodig om de productie van positieve symptomen te stoppen en voorkomen, maar dat pakt niet de onderliggende stoornis aan die de functionele beperkingen veroorzaakt en kan deze misschien verergeren.

Veel robuust bewijs van de effectiviteit van antipsychotica om positieve symptomen te stoppen en voorkomen

- Hogere relapse rates werden gevonden in alle trials die placebo met actieve medicatie vergeleken
- Robuust bewijs dat een langere duur van onbehandelde psychose een negatieve impact heeft op de prognose
- Bewijs is er dat dit ook opgaat voor de duur van de relapses

Rationale van onderhoudsbehandeling met antipsychotica

- Voorkomen van terugval positieve symptomen
- Behandeling met tussenpozen leidde steeds tot meer relapses op korte termijn
- Meer relapses treden op bij mensen met minder gunstige uitkomsten die vaker niet meer gevoelig zijn voor behandeling
- Maar zijn relapses de oorzaak van een slechte uitkomst, of zijn beide gevolgen van een ernstiger onderliggende stoornis?

Maar wat is er bekend over functionele uitkomsten?

- Er zijn bijna geen onderzoeksgegevens over functionele uitkomsten
- Symptomatische remissie leidt niet vanzelf tot functioneel herstel
- Negatieve symptomen kunnen verergeren door dopamine blokkade
- De integriteit van de hersenen kan misschien aangetast worden door antipsychotica

Oorspronkelijke discontinuatie trial

Hoofdvraag

Is onderhoudsbehandeling na remissie van een eerste episode psychose echt de beste optie?

We deden een RCT bij eerste episode psychose in remissie, om dosisreductie te vergelijken met onderhoudsbehandeling

We veronderstelden bij dosis-reductie/discontinuatie vergeleken met onderhoudsbehandeling:

Betere kwaliteit van leven en functioneren

Waarschijnlijk ten koste van:

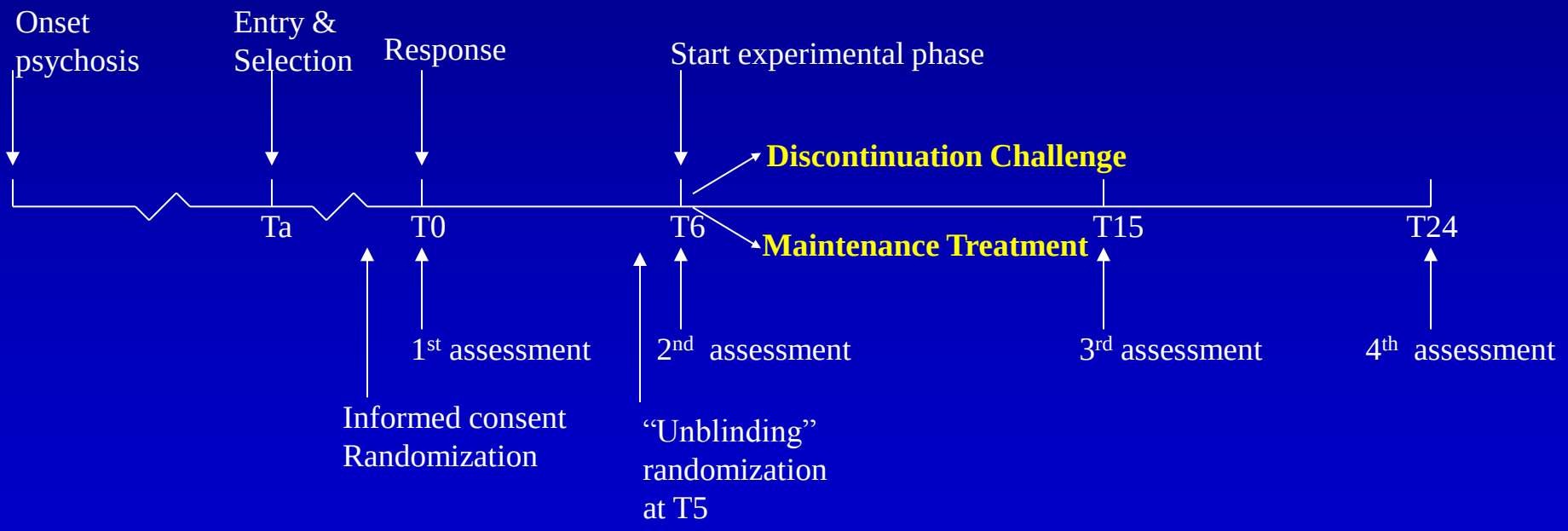
Meer relapses

Hoe werd de dosisverlagings/stopstrategie uitgevoerd?

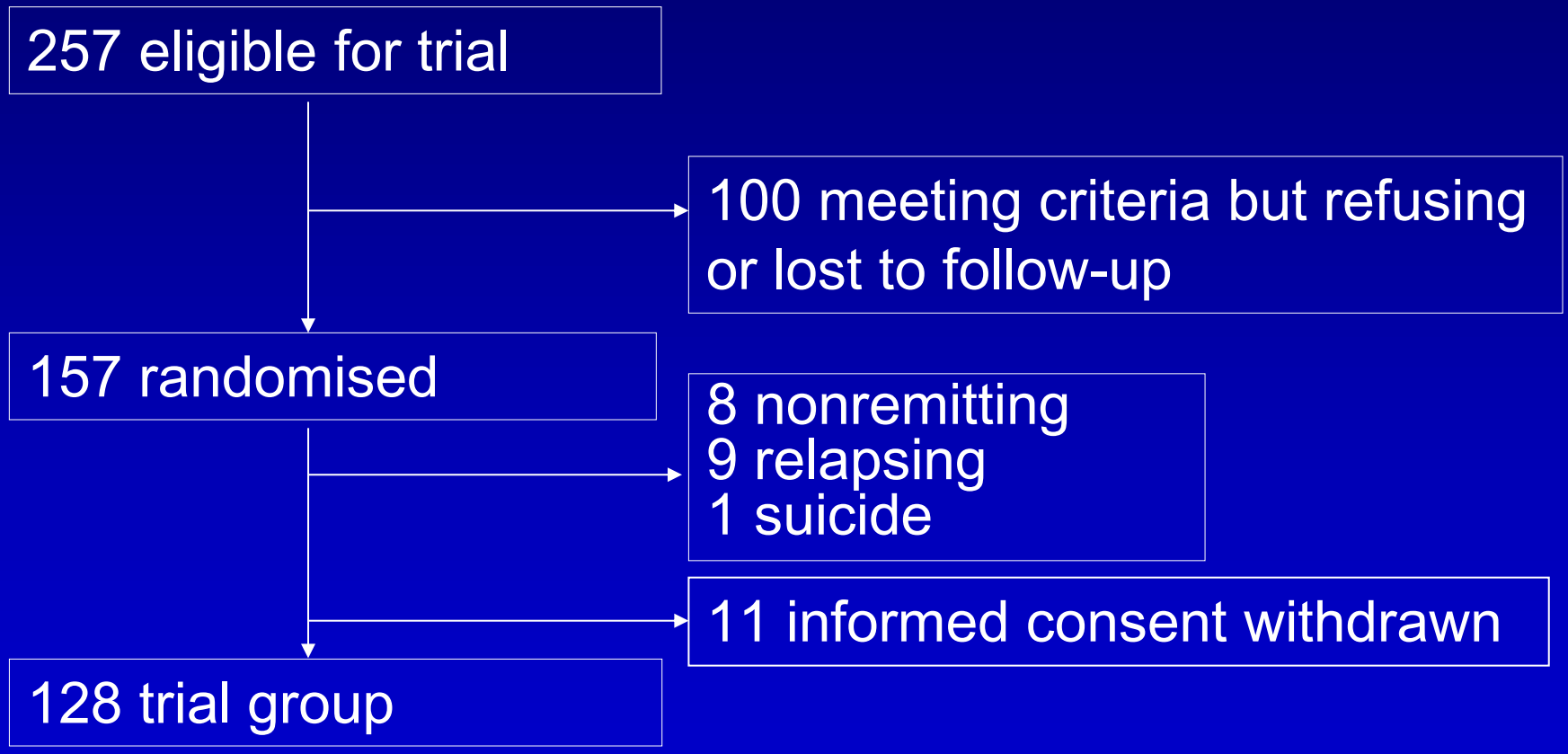
- Als de positieve symptomen waren verdwenen
- Verlagen van de dosering antipsychotica (met ongeveer 50%, afhankelijk van de begindosering)
- Monitoren van positieve symptomen
- Verder verlagen, tot tenslotte mogelijk stoppen
- Herstarten of dosisverhogen bij terugkerende positieve symptomen

Intention-to-treat, personalized approach, nauwe samenwerking met patiënt en familieleden.

Design of the study



Consort flow chart
Oct 2001 through Dec 2002



Wat vonden we na 2 jaar…

- Slechts 21.5% kon helemaal zonder antipsychotica
- Geen verschil in kwaliteit van leven tussen de armen
- Geen verschil in niveau van functioneren, maar wel meer aan het werk, net niet significant (35% vs. 17%, OR=2.4, *P = .06)*
- Twee keer zoveel relapses bij dosisverlaging in vergelijking met onderhoudsbehandeling: 42% tegen 21% in 18 maanden

Geen winst, wel meer relapses, hoewel die goedaardig waren en geen invloed hadden op opnamedagen of ernst van symptomen

7-years follow-up

- Doel: om het aantal herstelde patiënten te vergelijken
- Lange termijn effecten van dosisverlaging op herstel waren niet bekend
- 103 (80,5%) van 128 patiënten werden bereid gevonden mee te doen met de follow-up assessment
- Geen gecontroleerde behandeling in de tussentijd

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

Recovery, symptomatic and functional remission after 7 years

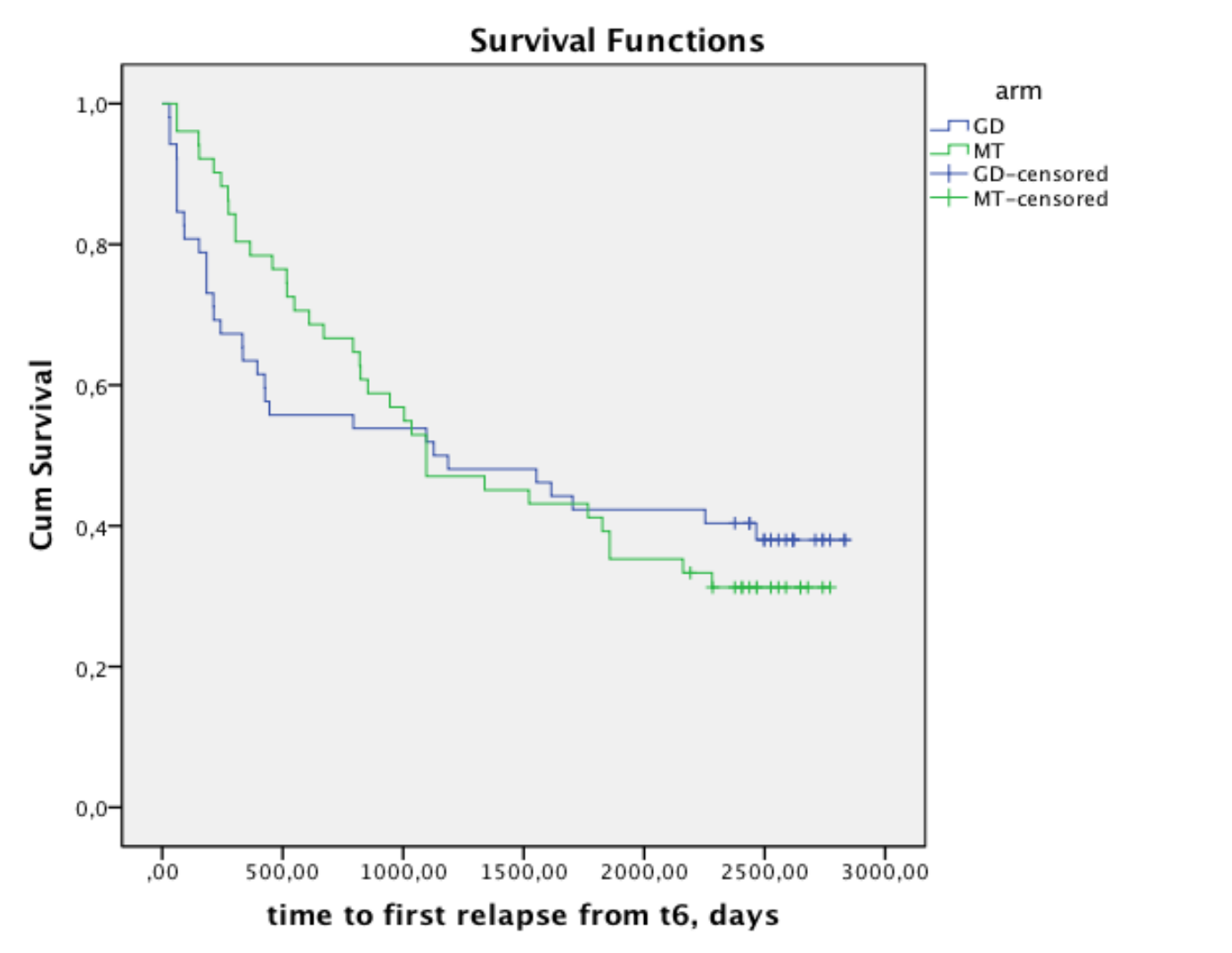
	DR (n=52)	MT (n=51)	Total sample (n=103)
Recovery	21 (40.4%)	9 (17.6%)	30 (29.1)
Symptom remission	36 (69.2%)	34 (66.7%)	70 (68.0)
Functional remission	24 (46.2%)	10 (19.6%)	34 (33.0)

Predictors of recovery, symptomatic and functional remission, logistic regression

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



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

Dosis-verlaging is het best!

- Dosisverlaging bij eerste episode patienten in remissie geeft twee maal zoveel herstel (40.4% vs. 17.6%)
- Geen verschil in symptoom remissie rates (69.2% vs. 66.7%)
- Hoewel relapse rates op korte termijn twee keer zo hoog waren, waren ze gelijk vanaf drie jaar follow-up (ongeveer 60% had tenminste1 relapse in 7 jaar)

Sla snel toe, maar laat de teugel vieren zodra de positieve symptomen het toelaten

- Behandel positieve symptomen zo snel mogelijk met antipsychotica
- Zodra de symptomen verdwenen zijn: verminder geleidelijk de belasting met antipsychotica zodanig dat de symptomen afwezig blijven
- Ga door met monitoren en pas zo mogelijk/zo nodig de dosering van antipsychotica aan

Waarom werkt dit?

- Verlichting van overbodige dopamine blokkade, die niet nodig is om de psychose te bestrijden, en die functionele beperkingen veroorzaakt
- Dat laat meer en beter functioneel herstel toe.

MESIFOS Researchteam

University Hospital Groningen

- Han Bous, research nurse
- Rikus Knegtering, psychiatrist
- Fokko Nienhuis, psychologist
- Minie Veenstra, research nurse
- Durk Wiersma, sociologist
- Lex Wunderink, psychiatrist

Mental Health Institute of Groningen

- Hans Klein, psychiatrist

Mental Health Institute of Friesland

- Nynke Boonstra, research nurse
- Peter Borghaerts, psychiatrist
- Jaap Kooistra, research nurse
- Domy van der Werf, psychiatrist

Mental Health Institute of Drenthe

- Marieke Pijnenborg, psychologist
- Margreet Schilthuis, research nurse
- Cees Slooff, psychiatrist
- Klaas-Pieter Touw, research nurse

Mental Health Institute of Twente

- Chris Albers, research nurse
- Eric Noorthoorn, researchphysician
- Roger Veldwijk, research nurse
- Pieter Vlaminck, psychiatrist
- Pieter de Wit, psychiatrist

Mental Health Institute of Midden-Overijssel

- Jolanda Brilman, research nurse
- Just van der Linde, psychiatrist
- Renate van der Valk, research nurse

Mental Health Institute of Gelderland-Oost

- Wim Janssen, research nurse
- Laura Kramer, psychologist
- Paul Oosterholt, research nurse
- Margriet de Ronde, research nurse

Mental Health Institute of Zuid-Holland Zuid-Oost

- Cor Anneveldt, research nurse
- Gunnar Faber, psychiatrist
- Sjaak van Gijzen, research nurse
- Rob Smit, psychiatrist