IX Congresso Nazionale
AIPP

Bari
27-28-29 Settembre 2023

Philippe Conus
Lausanne University Hospital

The future of early intervention in mental health

PLAN

- INTRODUCTION: Achievements of early intervention
- LIMITATIONS AND SOME WAYS FORWARD: Overcoming hurdles and challenges
  - Clinical domain
  - Neurobiological mechanisms
  - Political issues
  - Societal challenges
- CONCLUSIONS

PLAN

- INTRODUCTION: Achievements of early intervention
- LIMITATIONS AND SOME WAYS FORWARD: Overcoming hurdles and challenges
  - Clinical domain
  - Neurobiological mechanisms
  - Political issues
  - Societal challenges
- CONCLUSIONS

INTERVENTION IN MENTAL HEALTH
In the past…

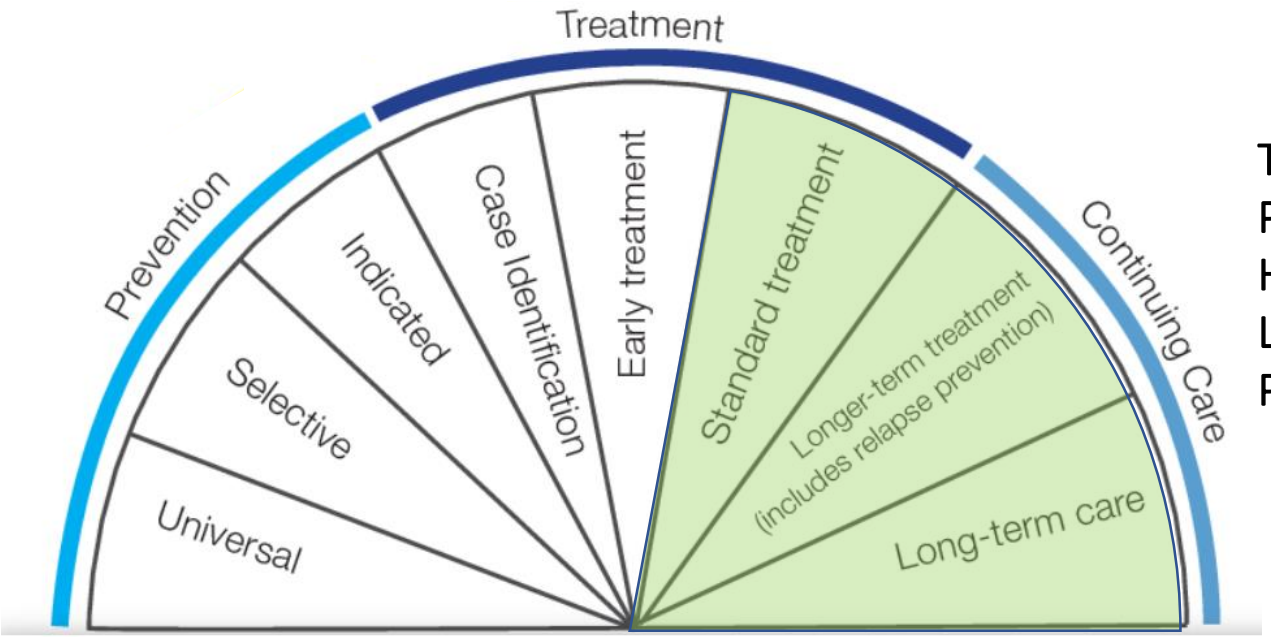


Figure 1: Mrazek & Haggerty's model of the spectrum of interventions for mental health problems and mental disorders50

Taking care of chronicity
Pesimistic approach
High stigma
Low empowerment of patients
Poor outcome…

INTERVENTION IN MENTAL HEALTH
1990: a need for change!


P Mcgorry

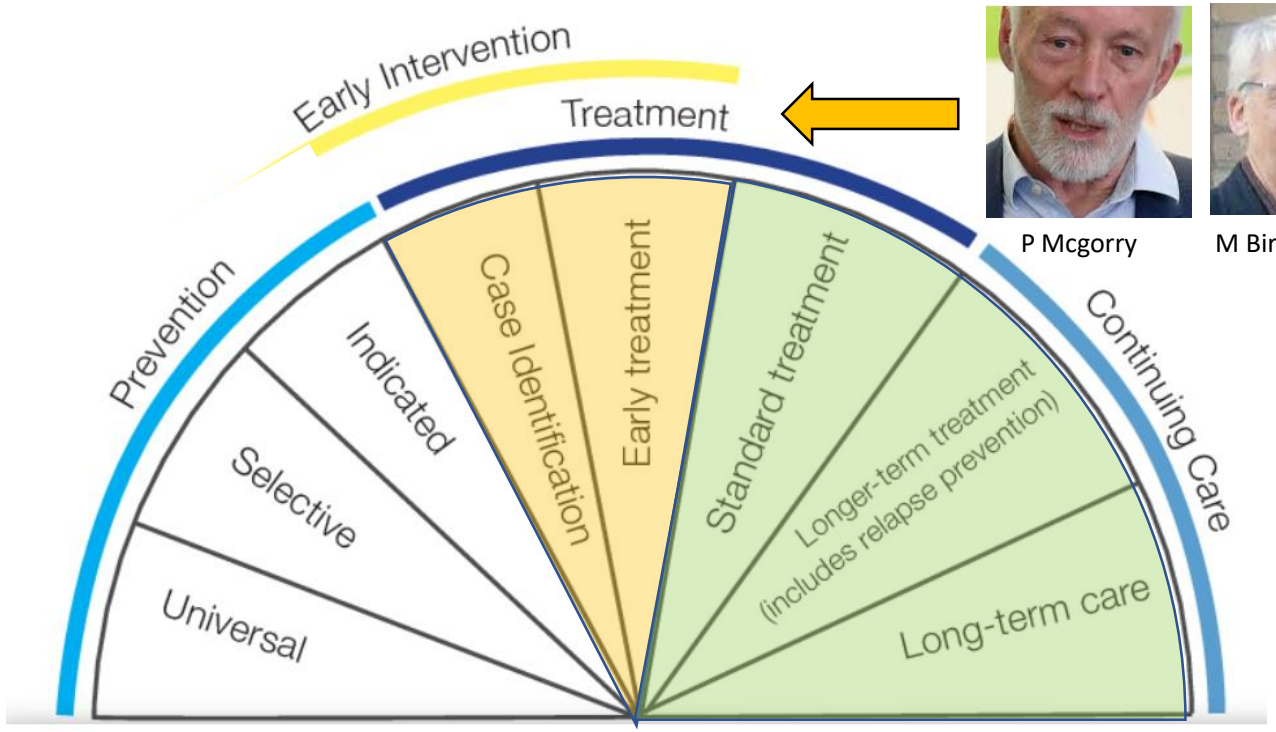

M Birchwood


M Nordentoft


JO Johannessen

Figure 1: Mrazek & Haggerty's model of the spectrum of interventions for mental health problems and mental disorders50

EARLY INTERVENTION IN MENTAL HEALTH



P Mcgorry

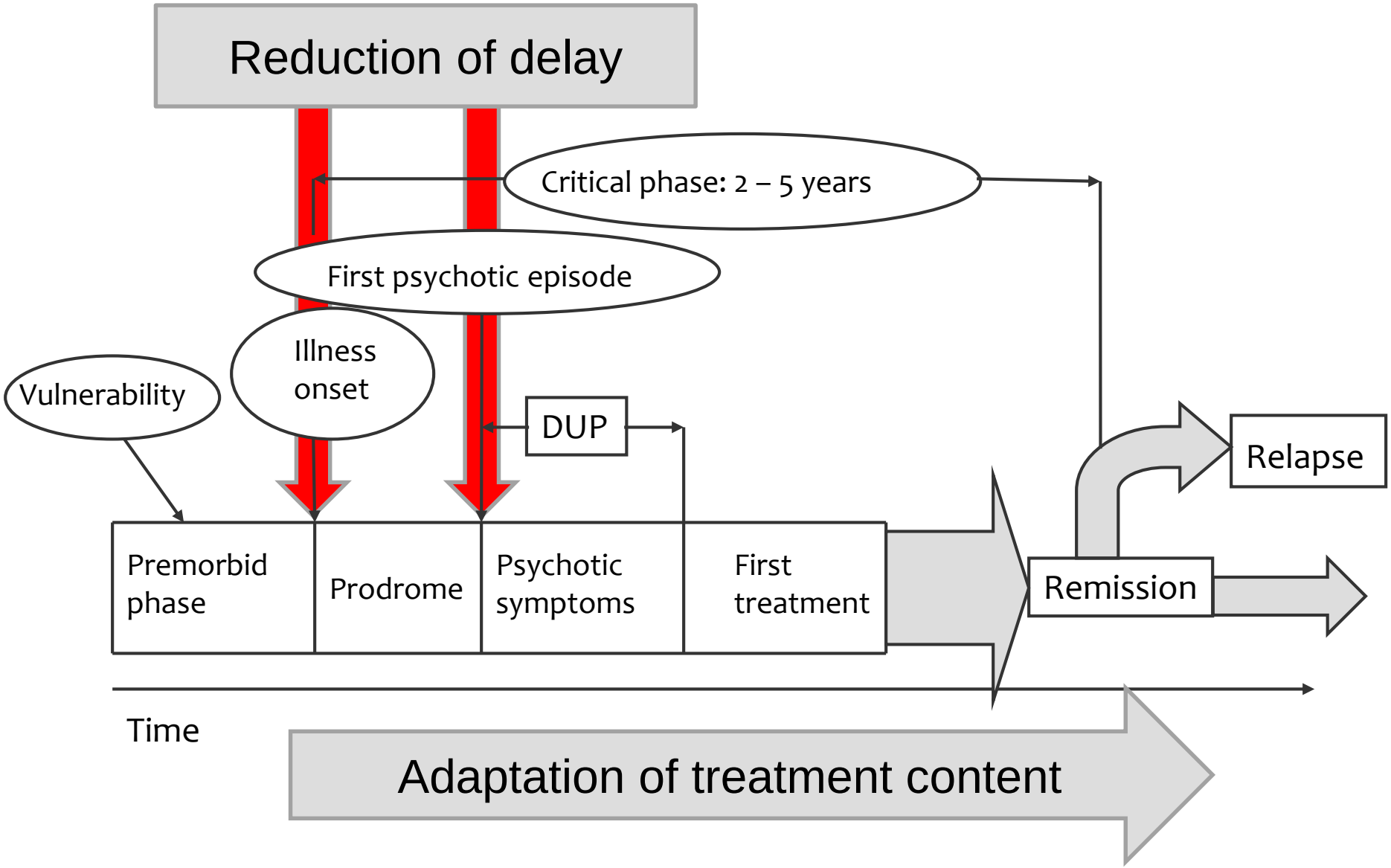

M Birchwood


M Nordentoft


JO Johannessen

Figure 1: Mrazek & Haggerty's model of the spectrum of interventions for mental health problems and mental disorders50

Targets and strategies of early intervention: the example of psychosis



The challenges in the early phase of psychosis

DENIAL

DISENGAGEMENT

First episode psychosis: patients' engagement in standard care is poor

MÉMOIRE ORIGINAL

Insertion dans les soins après une première hospitalisation dans un secteur pour psychose

C. BONSACK [1], T. PFISTER, P. CONUS

Linkage to care after first hospitalisation for psychosis

Summary. Background. *First hospitalisation for a psychotic episode causes intense distress to patients and families, but offers an opportunity to make a diagnosis and start treatment. However, linkage to outpatient psychiatric care remains a notoriously difficult step for young psychotic patients, who frequently interrupt treatment after hospitalisation. Persistence of symptoms, and untreated psychosis may therefore remain a problem despite hospitalisation and proper diagnosis. With persisting psychotic symptoms, numerous complications may arise : breakdown in relationships, loss of family and social support, loss of employment or study interruption, denial of disease, depression, suicide, substance abuse and violence. Understanding mechanisms that might promote linkage to outpatient psychiatric care is therefore a critical issue, especially in early intervention in psychotic disorders.* **Objective.** *To study which factors hinder or promote linkage of young psychotic patients to outpatient psychiatric care after a first hospitalisation, in the absence of a vertically integrated program for early psychosis.* **Method.** *File audit study of all patients aged 18 to 30 who were admitted for the first time to the psychiatric University Hospital of Lausanne in the year 2000. For statistical analysis, χ^2 tests were used for categorical variables and t-test for dimensional variables ; $p < 0.05$ was considered as statistically significant.* **Results.** *230 patients aged 18 to 30 were admitted to the Lausanne University psychiatric hospital for the first time during the year 2000, 52 of them with a diagnosis of psychosis (23 %). Patients with psychosis were mostly male (83 %) when compared with non-psychosis patients (49 %). Furthermore, they had (1) 10 days longer mean duration of stay (24 vs 14 days), (2) a higher rate of compulsory admissions (53 % vs 22 %) and (3) were more often hospitalised by a psychiatrist rather than by a general practitioner (83 % vs 53 %). Other socio-demographic and clinical features at admission were similar in the two groups. Among the 52 psychotic patients, 10 did not stay in the catchment area for subsequent treatment. Among the 42 psychotic patients who remained in the catchment area after discharge, 20 (48 %) did not attend the scheduled or rescheduled outpatient appointment. None of the socio demographic characteristics were associated with attendance to outpatient appointments. On the other hand, voluntary admission and suicidal ideation before admission were significantly related to attending the initial appointment. Moreover, some elements of treatment seemed to be associated with higher likelihood to attend outpatient treatment : (1) provision of information to the patient regarding diagnosis, (2) discussion about the treatment plan between in- and outpatient staff, (3) involvement of outpatient team during hospitalisation, and (4) elaboration of concrete strategies to face basic needs, organise daily activities or education and reach for help in case of need.* **Conclusion.** *As in other studies, half of the patients admitted for a first psychotic episode failed to link to outpatient psychiatric care. Our study suggests that treatment rather than patient's characteristics play a critical role in this phenomenon. Development of a partnership and involvement of patients in the decision process, provision of good information regarding the illness, clear definition of the treatment plan, development of concrete strategies to cope with the illness and its potential complications, and involvement of the outpatient treating team already during hospitalisation, all came out as critical strategies to facilitate adherence to outpatient care. While the current rate of disengagement after admission is highly concerning, our finding are encouraging since they constitute strategies that can easily be implemented. An open approach to psychosis, the development of partnership with patients and a better coordination between inpatient*

(1) Département Universitaire de Psychiatrie Adulte, Site de Cery, 1008 Prilly – Lausanne, Suisse.

Travail reçu le 7 octobre 2004 et accepté le 9 mai 2005.

Tirés à part : C. Bonsack (à l'adresse ci-dessus).

After a first hospitalisation for psychosis, in the absence of a specific organisation of care :

- **50% of patients never attend** first out-patient appointment after discharge
- **Of those who attend, 50% disengage** after 2 appointments
- **Readmission occurs within the year**

The strategies

- REDUCING DISENGAGEMENT:
  - **Promoting engagement**: the central role of case managers
  - **Identifying patients at risk of disengagement**
  - **Increasing accessibility**: mobile teams, assertive attitude

- PROMOTING INSIGHT:
  - **Empowerment**
  - **Optimism**
  - **Partnership**
  - **Focusing on resources and not only on difficulties and symptoms**

The strategies

- REDUCING DISENGAGEMENT:
  - **Promoting engagement**: the central role of case managers
  - **Identifying patients at risk of disengagement**
  - **Increasing accessibility**: mobile teams, assertive attitude

- PROMOTING INSIGHT:
  - **Empowerment**
  - **Optimism**
  - **Partnership**
  - **Focusing on resources and not only on difficulties and symptoms**

1. Promoting engagement: a matter of attitude

INTERVENTION INSIGHTS

The therapeutic alliance: is it necessary or sufficient to engender positive outcomes?

Craig A. Macneil[1], Melissa K. Hasty[1], Melanie Evans[1], Cassie Redlich[1], Michael Berk[1,2,3,4]

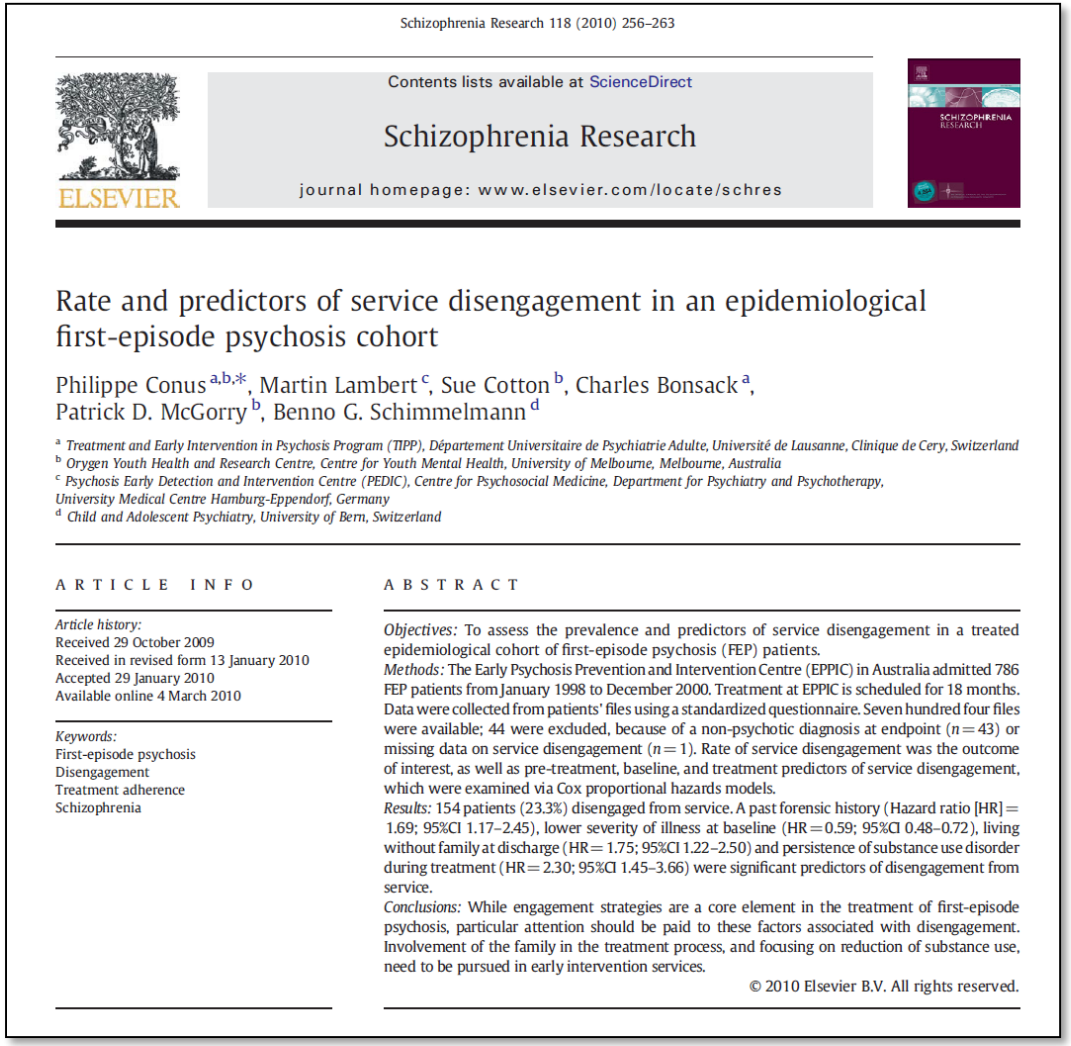
Acta Neuropsychiatrica 2009: 2:95–98

1. Promoting engagement

1. Take time to **understand the whole person** rather than focus only on psychopathology
2. Understand the **person's explanatory model**
3. Enquire about **patient's previous experience** of treatment
4. **Explore strengths and hopes** and not only difficulties
5. **Tailor intervention to patient's stage** of recovery
6. **Plan treatment** on the basis of **patients' priorities**
7. Encourage **realistic hopes** and **optimism**

8. Be prepared for ruptures which can be a fertile ground
9. Engagement is an ongoing process: it takes time and perseverance
10. Let patients matter to you

2. Identifying patients at risk of disengagement



Schizophrenia Research 118 (2010) 256–263

Contents lists available at ScienceDirect

Schizophrenia Research

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

Rate and predictors of service disengagement in an epidemiological first-episode psychosis cohort

Philippe Conus [a,b,*], Martin Lambert [c], Sue Cotton [b], Charles Bonsack [a], Patrick D. McGorry [b], Benno G. Schimmelmann [d]

[a] Treatment and Early Intervention in Psychosis Program (TIPP), Département Universitaire de Psychiatrie Adulte, Université de Lausanne, Clinique de Cery, Switzerland
[b] Orygen Youth Health and Research Centre, Centre for Youth Mental Health, University of Melbourne, Melbourne, Australia
[c] Psychosis Early Detection and Intervention Centre (PEDIC), Centre for Psychosocial Medicine, Department for Psychiatry and Psychotherapy, University Medical Centre Hamburg-Eppendorf, Germany
[d] Child and Adolescent Psychiatry, University of Bern, Switzerland

ARTICLE INFO

Article history:
Received 29 October 2009
Received in revised form 13 January 2010
Accepted 29 January 2010
Available online 4 March 2010

Keywords:
First-episode psychosis
Disengagement
Treatment adherence
Schizophrenia

ABSTRACT

Objectives: To assess the prevalence and predictors of service disengagement in a treated epidemiological cohort of first-episode psychosis (FEP) patients.
Methods: The Early Psychosis Prevention and Intervention Centre (EPPIC) in Australia admitted 786 FEP patients from January 1998 to December 2000. Treatment at EPPIC is scheduled for 18 months. Data were collected from patients' files using a standardized questionnaire. Seven hundred four files were available; 44 were excluded, because of a non-psychotic diagnosis at endpoint ($n=43$) or missing data on service disengagement ($n=1$). Rate of service disengagement was the outcome of interest, as well as pre-treatment, baseline, and treatment predictors of service disengagement, which were examined via Cox proportional hazards models.
Results: 154 patients (23.3%) disengaged from service. A past forensic history (Hazard ratio [HR] = 1.69; 95%CI 1.17–2.45), lower severity of illness at baseline (HR = 0.59; 95%CI 0.48–0.72), living without family at discharge (HR = 1.75; 95%CI 1.22–2.50) and persistence of substance use disorder during treatment (HR = 2.30; 95%CI 1.45–3.66) were significant predictors of disengagement from service.
Conclusions: While engagement strategies are a core element in the treatment of first-episode psychosis, particular attention should be paid to these factors associated with disengagement. Involvement of the family in the treatment process, and focusing on reduction of substance use, need to be pursued in early intervention services.

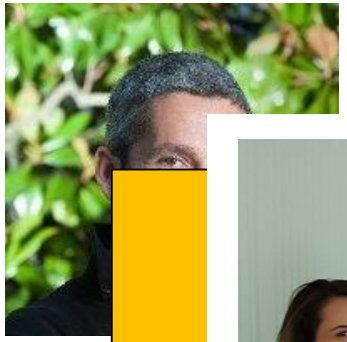
- *DISENGAGEMENT PREVALENCE over 18 months:* ***23%***

- *PREDICTIVE FACTORS (Cox regression)*
  - *Past forensic history (HR = 1.7)*
  - *No contact with family (HR = 1.7)*
  - *Persistance of Substance abuse (HR= 2.3)*

- *STRATEGIES*
  - *Specific attention to patients with forensic issues*
  - *Work with families*
  - *Work on addiction*

3. Organizing care to facilitate access

TIPP : Treatment and early Intervention in Psychosis Program



Stéph

Families
GP
Psychiat
Emerger
Schools

ed

Alessandra Solida

%

HARGE
ment
ution
psy

Hospital unit

The strategies

- REDUCING DISENGAGEMENT:
  - **Promoting engagement**: the central role of the case managers
  - **Identifying patients at risk of disengagement**
  - **Increasing accessibility**: mobile teams, assertive attitude

- PROMOTING INSIGHT:
  - **Empowerment**
  - **Optimism**
  - **Partnership**
  - **Focusing on resources and not only on difficulties and symptoms**

The strategies

- REDUCING DISENGAGEMENT:
  - **Promoting engagement**: the central role of the case managers
  - **Identifying patients at risk of disengagement**
  - **Increasing accessibility**: mobile teams, assertive attitude

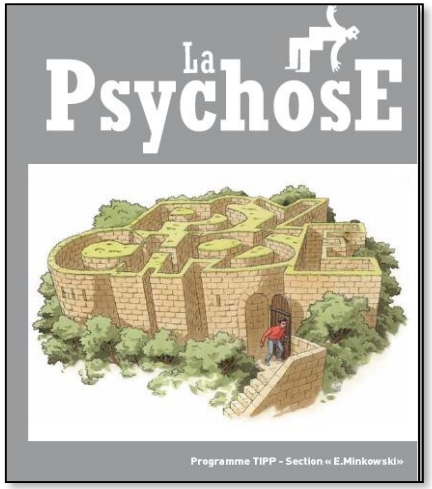
- PROMOTING INSIGHT:
  - **Empowerment**
  - **Optimism**
  - **Partnership**
  - **Focusing on resources and not only on difficulties and symptoms**

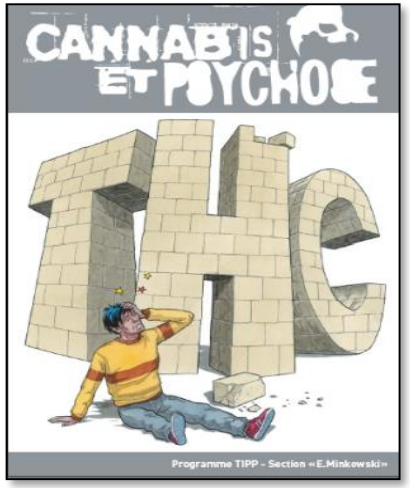
Promoting insight

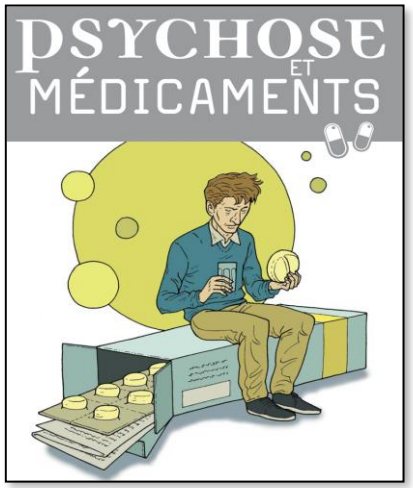
- A collaborative process: psycho-education is only one element
- Not an emergency!
- Can sometimes do more harm than good: adapt intervention to each patient's stage of recovery
- **Development of insight is a psychotherapeutic process in itself**

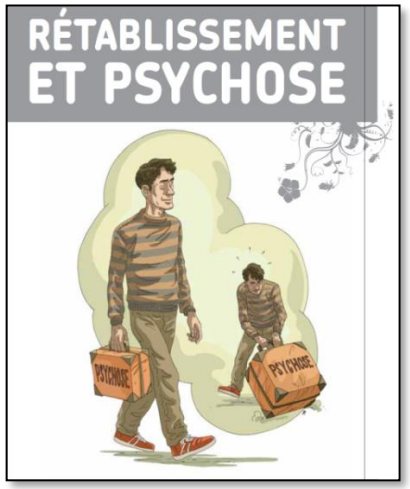
- **Main elements:**
  - *Listen to the patient, to their conception of what is happening*
  - *Define objectives that suit them*
  - *Do not directly question denial*
  - *Explore and try to understand the possible meaning of delusions*
  - *Identify crisis factors*
  - *Listen, propose alternative conceptions to explain crisis*
  - *Be flexible, accept partial insight, accept variations in degree of insight over time*

Collaborative psycho-education manuals









What is the impact and the cost of such programs?

Is Ealry Intervention in Psychosis Cost-Effective Over The Long Term?

Schizophrenia Bulletin vol. 35 no. 5 pp. 909–918, 2009
doi:10.1093/schbul/sbp054
Advance Access publication on June 9, 2009

Cathrine Mihalopoulos[1,2], Meredith Harris[3], Lisa Henry[4,5], Susy Harrigan[4,5], and Patrick McGorry[4,5]

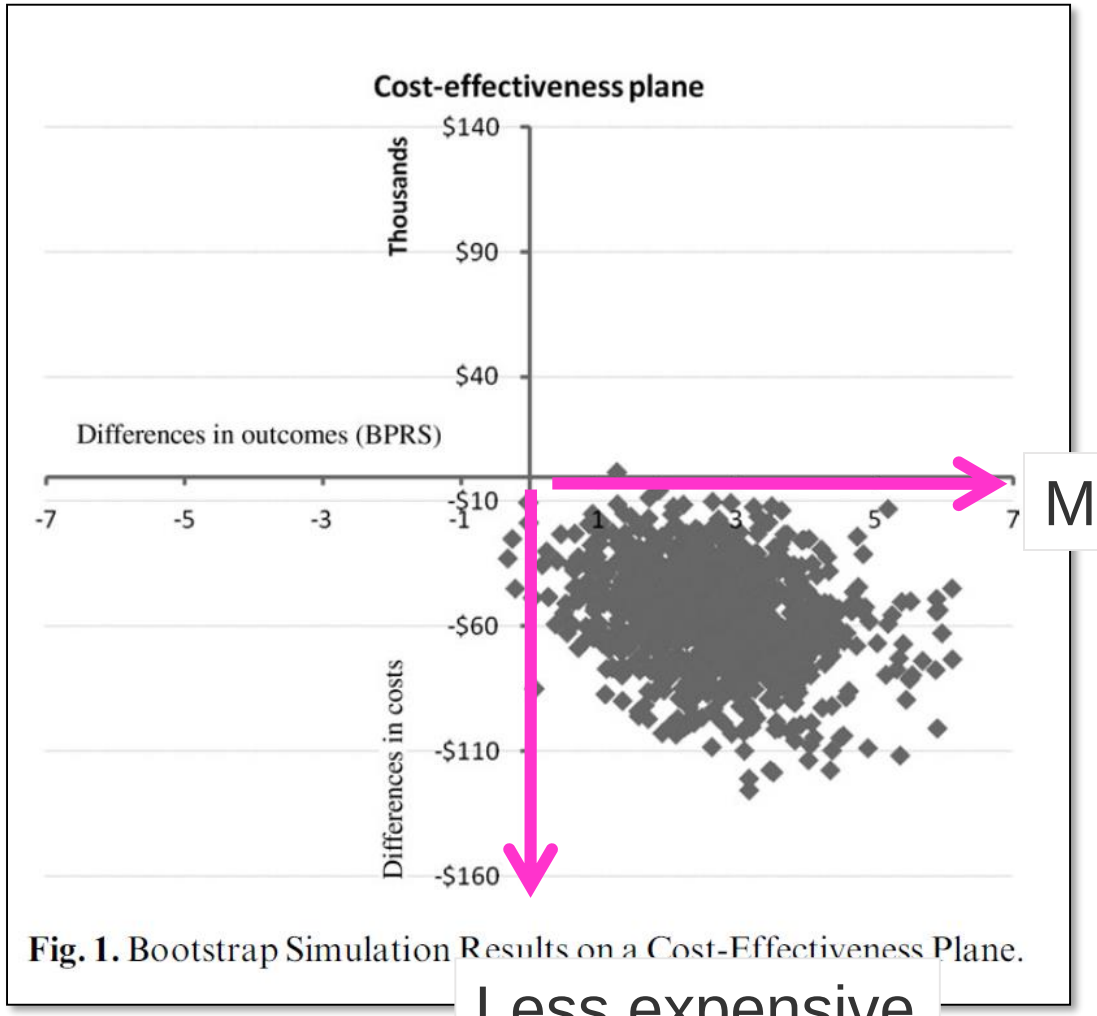
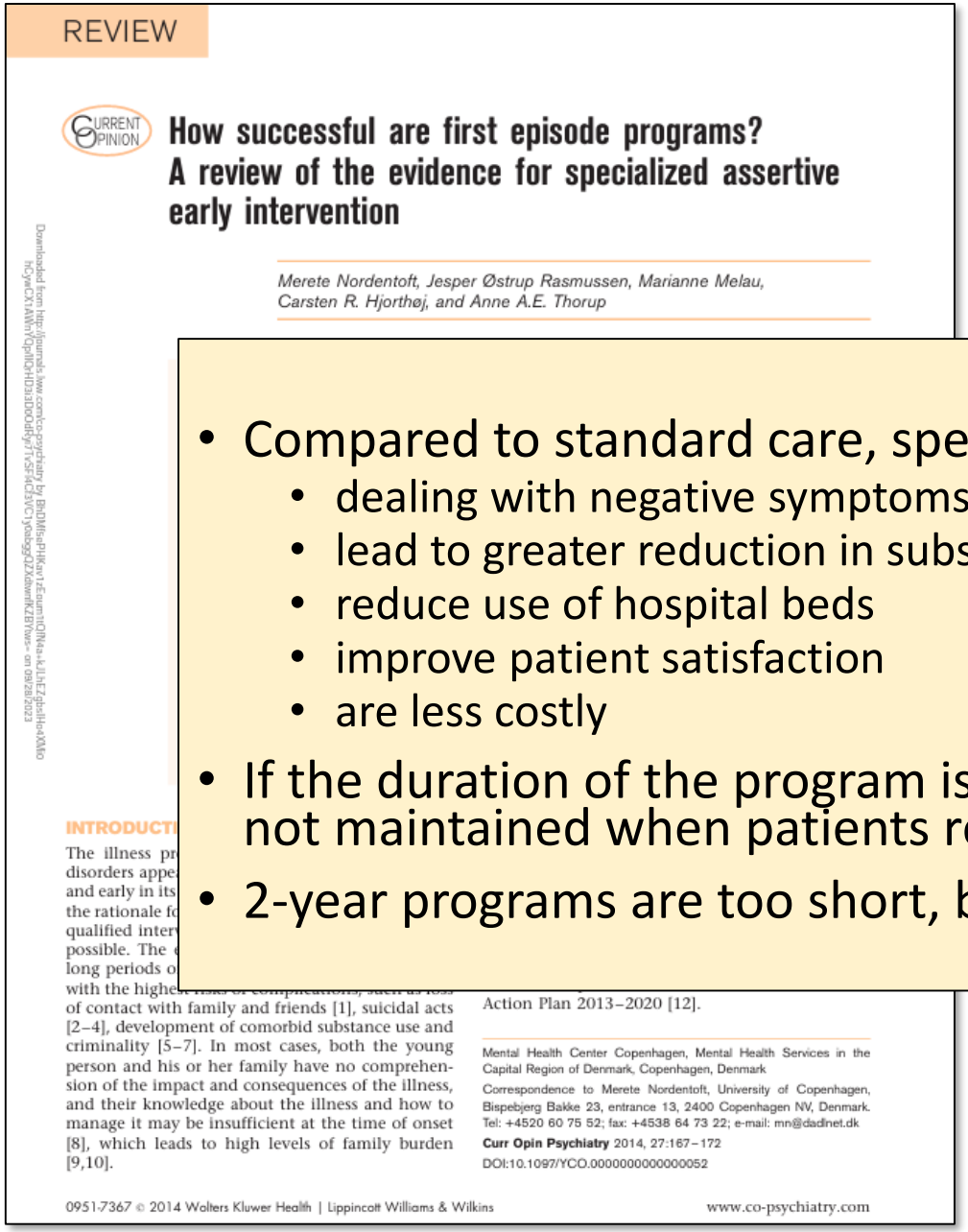


Fig. 1. Bootstrap Simulation Results on a Cost-Effectiveness Plane.



REVIEW

CURRENT OPINION

How successful are first episode programs? A review of the evidence for specialized assertive early intervention

Merete Nordentoft, Jesper Østrup Rasmussen, Marianne Melau, Carsten R. Hjorthøj, and Anne A.E. Thorup

The illness pr
disorders appe
and early in its
the rationale fo
qualified interv
possible. The
long periods o
with the highe
of contact with family and friends [1], suicidal acts [2–4], development of comorbid substance use and criminality [5–7]. In most cases, both the young person and his or her family have no comprehension of the impact and consequences of the illness, and their knowledge about the illness and how to manage it may be insufficient at the time of onset [8], which leads to high levels of family burden [9,10].

Action Plan 2013–2020 [12].

Mental Health Center Copenhagen, Mental Health Services in the Capital Region of Denmark, Copenhagen, Denmark

Correspondence to Merete Nordentoft, University of Copenhagen, Bispebjerg Bakke 23, entrance 13, 2400 Copenhagen NV, Denmark. Tel: +4520 60 75 52; fax: +4538 64 73 22; e-mail: mn@dadlnet.dk

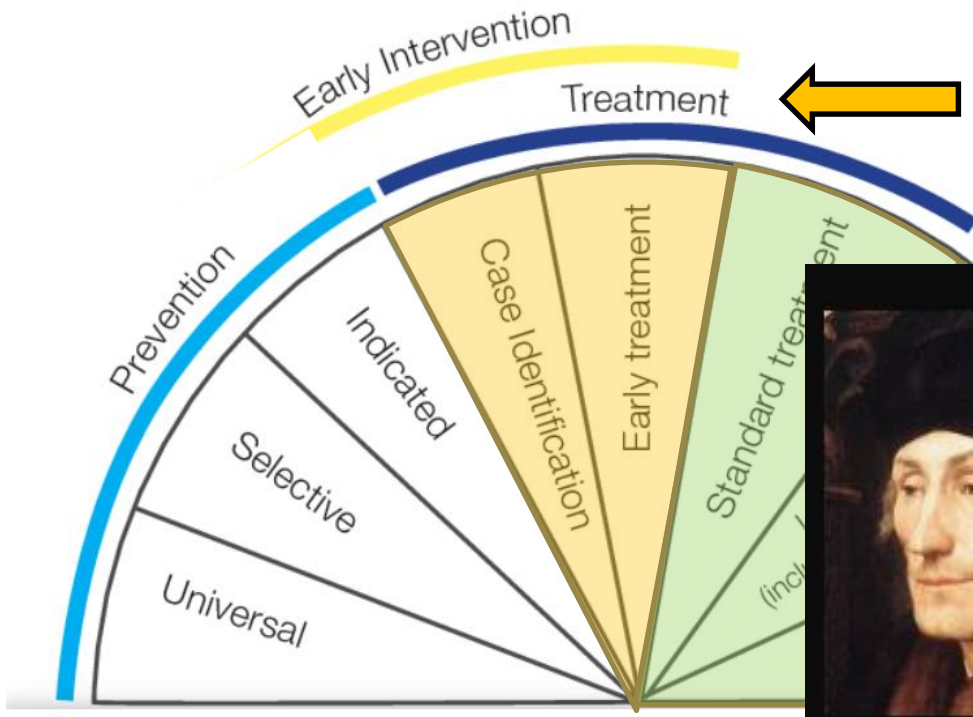
Curr Opin Psychiatry 2014, 27:167–172
DOI:10.1097/YCO.0000000000000052

www.co-psychiatry.com

- Compared to standard care, specialized programs are more effective in
  - dealing with negative symptoms
  - lead to greater reduction in substance abuse
  - reduce use of hospital beds
  - improve patient satisfaction
  - are less costly
- If the duration of the program is too short, these benefits are unfortunately not maintained when patients return to regular care.
- 2-year programs are too short, but the ideal duration has yet to be defined

Curr Opin Psychiatry 2014, 27:167–172

EARLY INTERVENTION IN MENTAL HEALTH




P Mcgorry


M Birchwood


M Nordentoft


JO Johannessen

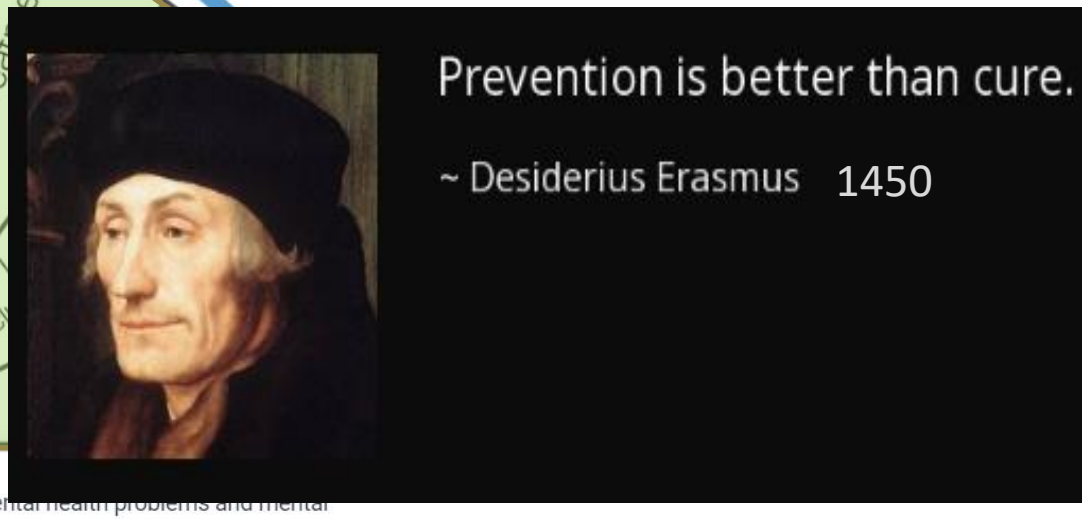


Figure 1: Mrazek & Haggerty's model of the spectrum of interventions for mental health problems and mental disorders50

EARLIER INTERVENTION IN MENTAL HEALTH

Alison Yung

Pat McGorry

Scott Woods

Barnaby Nelson

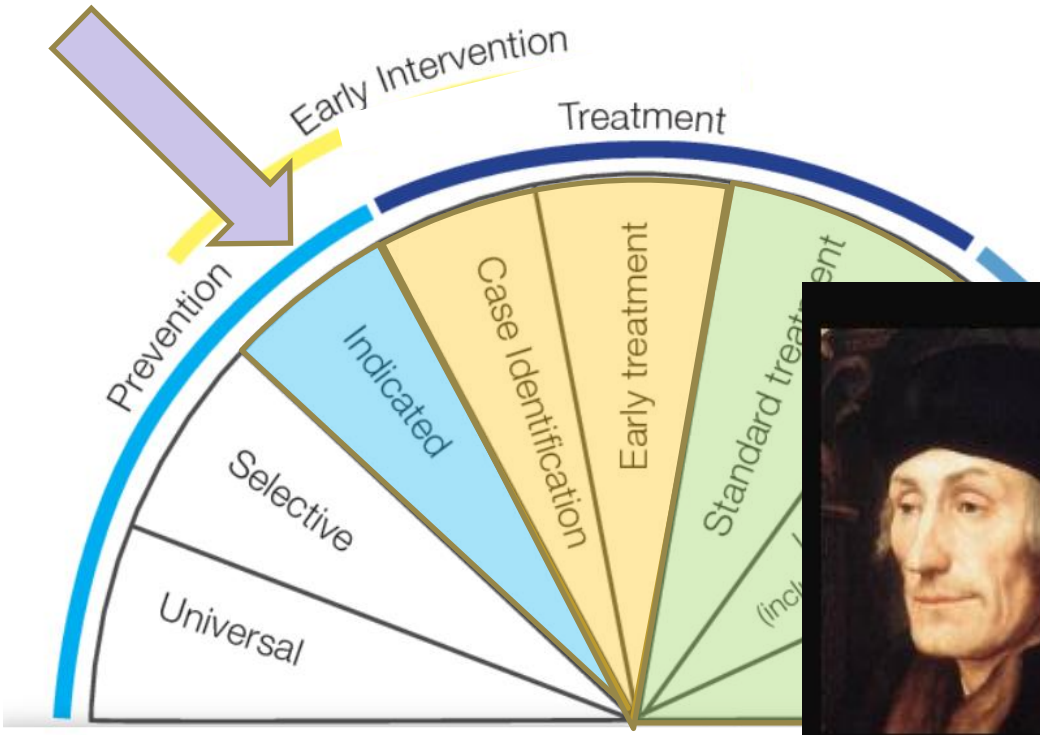
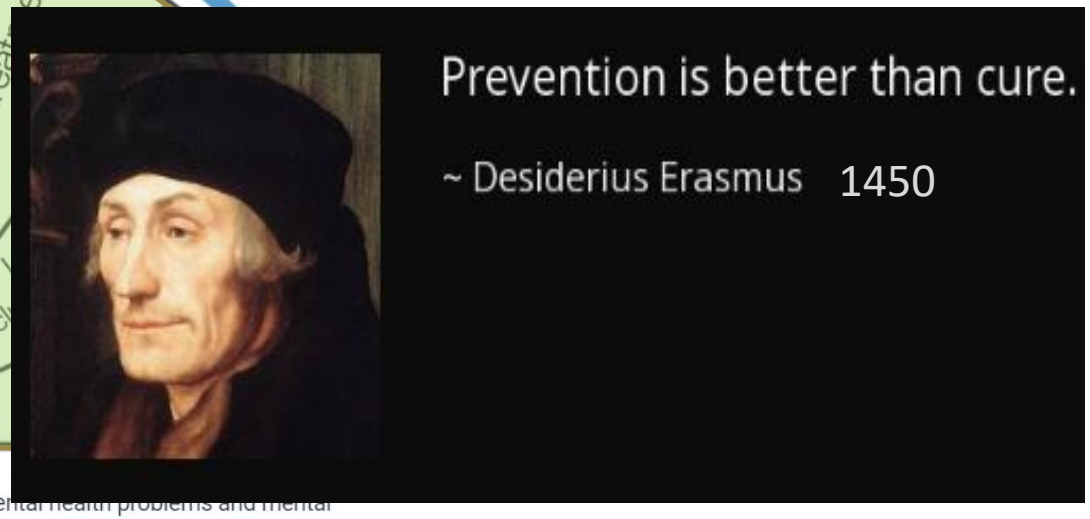


Figure 1: Mrazek & Haggerty's model of the spectrum of interventions for mental health problems and mental disorders50



THE PRODROMAL PHASE – AT Risk Mental State

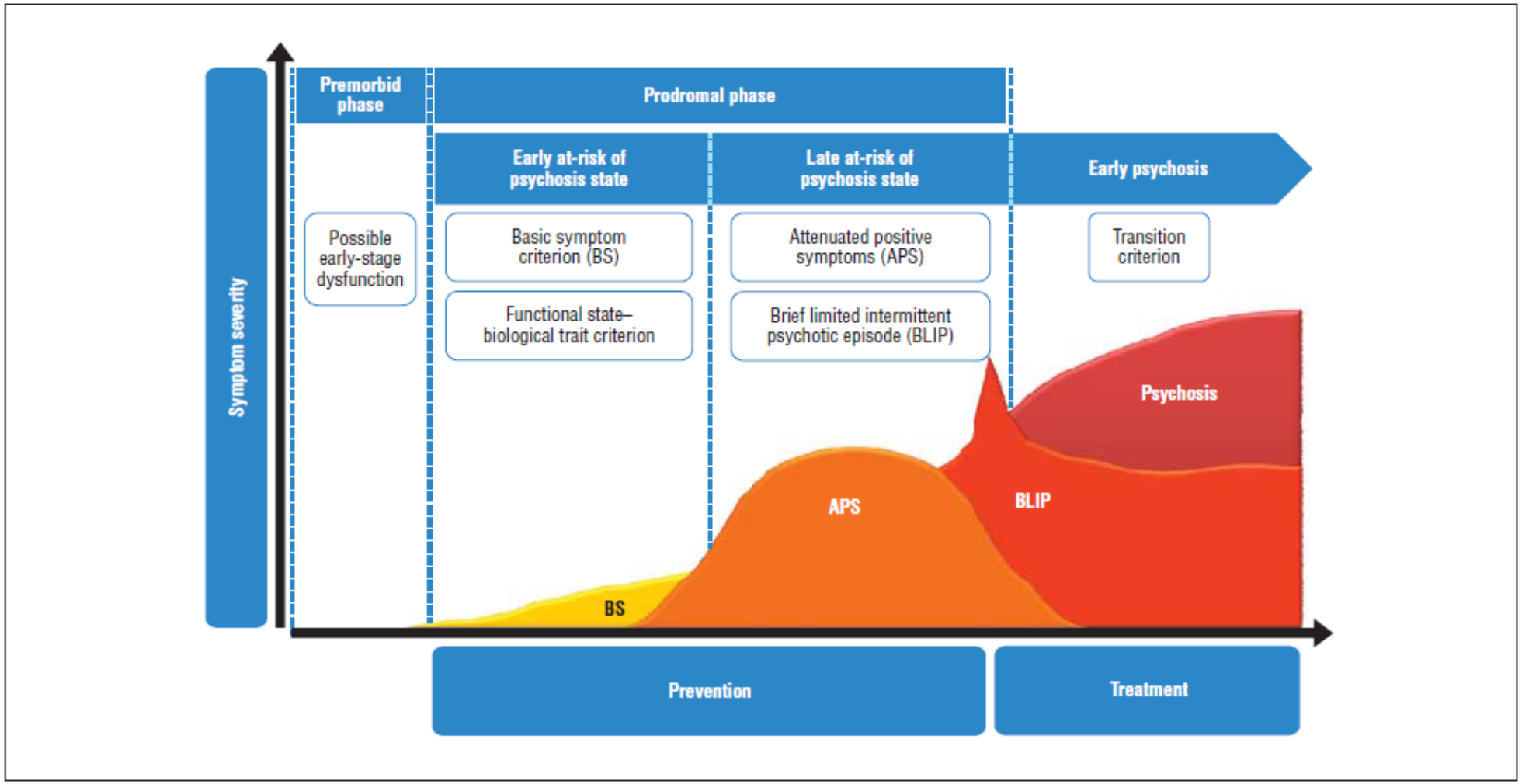


Figure 3. Model of psychosis onset from the clinical high-risk state. The higher the line on the y-axis, the higher the symptom severity.

Predicitve validity: transition rate to psychosis over time

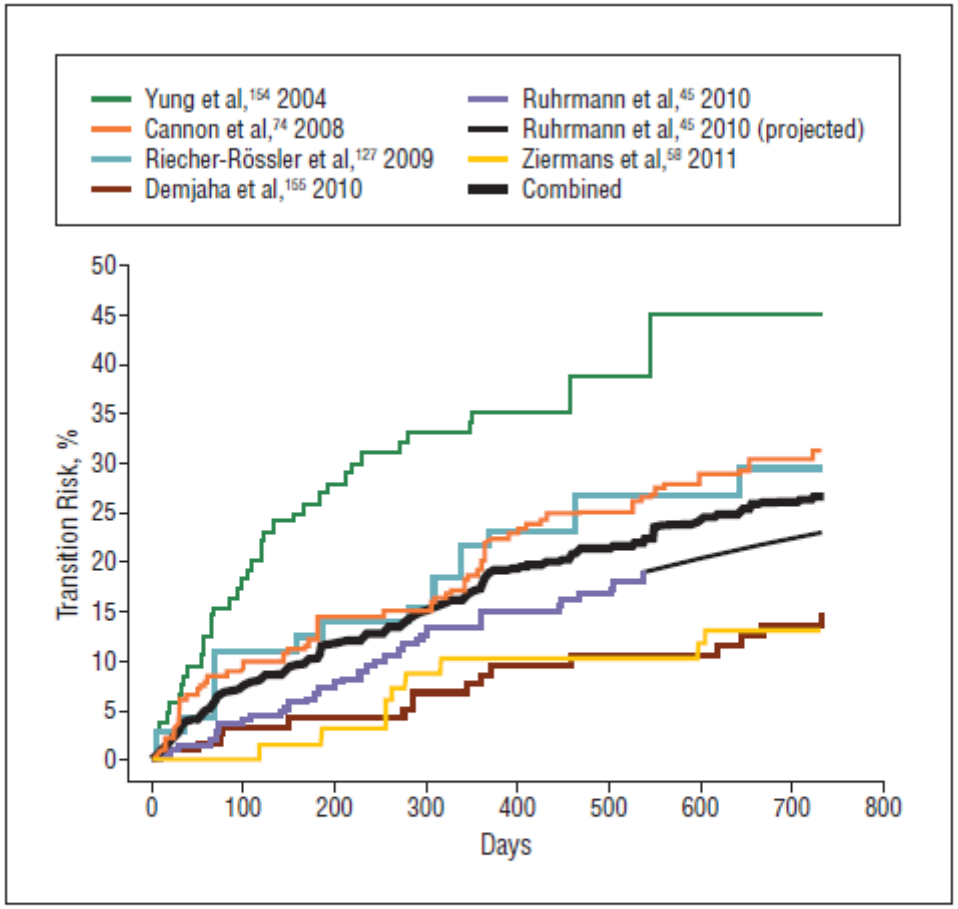


Figure 4. Meta-analysis of transition risks in studies reporting Kaplan-Meier estimates of psychosis transition over time in the high-risk state (n = 984 individuals) (for details of the study, see Fusar-Poli et al[75]). These risks are based on treated cohorts with no standardized treatment, so transition risk estimates are not for natural course or untreated cases.

Metanalysis on 2500 ARMS patients *(Fusar-Poli 2013)* :

6 months	18%
12 months	22%
24 months	32%
36 months	36%

Development of preventive treatments

ORIGINAL ARTICLE

Long-Chain ω-3 Fatty Acids for Indicated Prevention of Psychotic Disorders

A Randomized, Placebo-Controlled Trial

G. Paul Amminger, MD; Miriam R. Schäfer, MD; Konstantinos Papageorgiou, MD; Claudia M. Klier, MD; Sue M. Cotton, PhD; Susan M. Harrigan, MSc; Andrew Mackinnon, PhD; Patrick D. McGorry, MD, PhD; Gregor E. Berger, MD

Context: The use of antipsychotic medication for the prevention of psychotic disorders is controversial. Long-chain ω-3 (omega-3) polyunsaturated fatty acids (PUFAs) may be beneficial in a range of psychiatric conditions, including schizophrenia. Given that ω-3 PUFAs are generally beneficial to health and without clinically relevant adverse effects, their preventive use in psychosis merits investigation.

Objective: To determine whether ω-3 PUFAs reduce the rate of progression to first-episode psychotic disorder in adolescents and young adults aged 13 to 25 years with subthreshold psychosis.

Design: Randomized, double-blind, placebo-controlled trial conducted between 2004 and 2007.

Setting: Psychosis detection unit of a large public hospital in Vienna, Austria.

Participants: Eighty-one individuals at ultra-high risk of psychotic disorder.

Interventions: A 12-week intervention period of 1.2-g/d ω-3 PUFA or placebo was followed by a 40-week monitoring period; the total study period was 12 months.

Main Outcome Measures: The primary outcome measure was transition to psychotic disorder. Secondary outcomes included symptomatic and functional changes. The ratio of ω-6 to ω-3 fatty acids in erythrocytes was used to index pretreatment vs posttreatment fatty acid composition.

Results: Seventy-six of 81 participants (93.8%) completed the intervention. By study's end (12 months), 2 of 41 individuals (4.9%) in the ω-3 group and 11 of 40 (27.5%) in the placebo group had transitioned to psychotic disorder ($P=.007$). The difference between the groups in the cumulative risk of progression to full-threshold psychosis was 22.6% (95% confidence interval, 4.8-40.4). ω-3 Polyunsaturated fatty acids also significantly reduced positive symptoms ($P=.01$), negative symptoms ($P=.02$), and general symptoms ($P=.01$) and improved functioning ($P=.002$) compared with placebo. The incidence of adverse effects did not differ between the treatment groups.

Conclusions: Long-chain ω-3 PUFAs reduce the risk of progression to psychotic disorder and may offer a safe and efficacious strategy for indicated prevention in young people with subthreshold psychotic states.

Trial Registration: clinicaltrials.gov Identifier: NCT00396643

Arch Gen Psychiatry. 2010;67(2):146-154

Author Affiliations: Department of Child and Adolescent Psychiatry, Medical University of Vienna, Vienna, Austria (Drs Amminger, Schäfer, Papageorgiou, and Klier); Orygen Research Centre, Centre for Youth Mental Health, The University of Melbourne, Melbourne, Australia (Drs Amminger, Cotton, Mackinnon, and McGorry and Ms Harrigan); and Department of Research and Education, The Schlössli Clinic, Oetwil am See, Switzerland (Dr Berger).

EARLY TREATMENT IN SCHIZOphrenia and other psychoses has been linked to better outcomes.[1] Given that subclinical psychotic symptoms may predict psychotic disorder[2] and psychosis proneness in a population may be related to the rate of psychotic disorder,[3,4] intervention in at-risk individuals holds the promise of even better outcomes, with the potential to prevent full-blown psychotic disorders.

In the 1990s, a series of prospective studies validated criteria that are capable of identifying individuals with subthreshold symptoms at ultra-high risk of psychosis.[5] Neuroanatomical changes observed in ultra-high-risk individuals who progress to psychotic disorder suggest an active biological process during this transition, raising the possibility that intervention might be indicated before expression of frank psychotic symptoms.[6] To date, 3 randomized controlled studies have evaluated the efficacy of antipsychotic medication and/or cognitive therapy to reduce the conversion to psychosis rate in ultra-high-risk groups.[7-9] These studies support the ongoing evaluation of interventions for the prevention of conversion to psychosis.[10]

Based on findings of reduced long-chain ω-3 and ω-6 polyunsaturated fatty

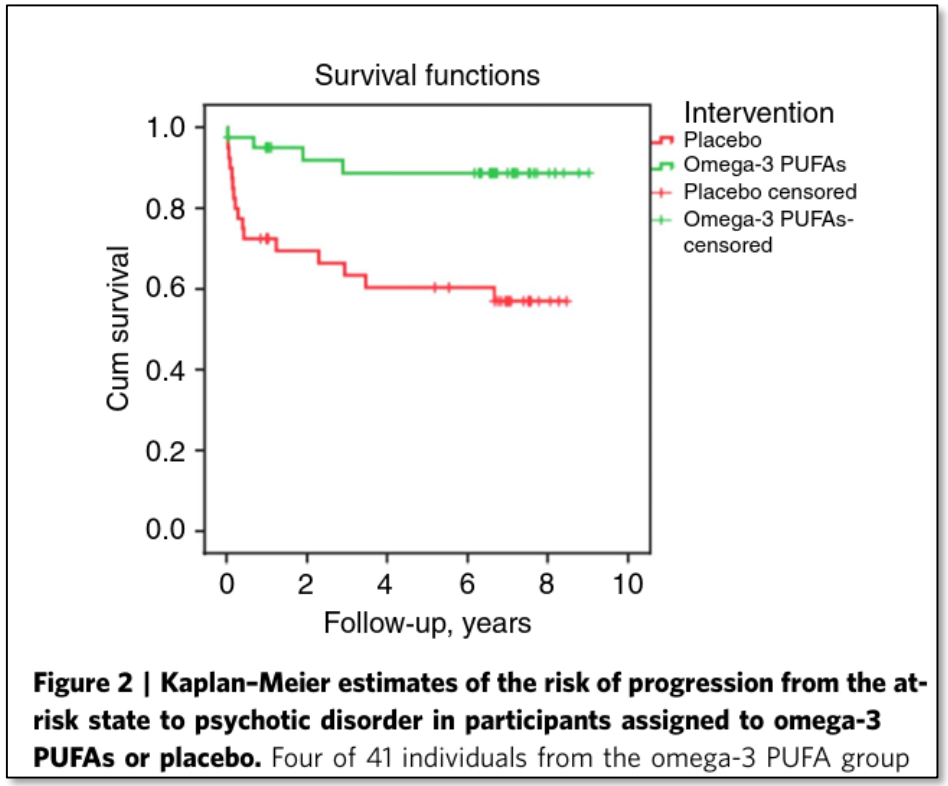


Figure 2 | Kaplan–Meier estimates of the risk of progression from the at-risk state to psychotic disorder in participants assigned to omega-3 PUFAs or placebo. Four of 41 individuals from the omega-3 PUFA group

In summary

- Has been a major improvement and a revolution in the way we approach psychiatry
  - Hope
  - Ambition
  - Empowerment
- Has majorly impacted
  - Quality and efficacy of treatment
  - The availability of secondary and tertiary prevention strategies
- Has promoted a huge intersest in research

National Library of Medicine
National Center for Biotechnology Information

Log in

PubMed®

early intervention AND psychosis

Search

Advanced Create alert Create RSS

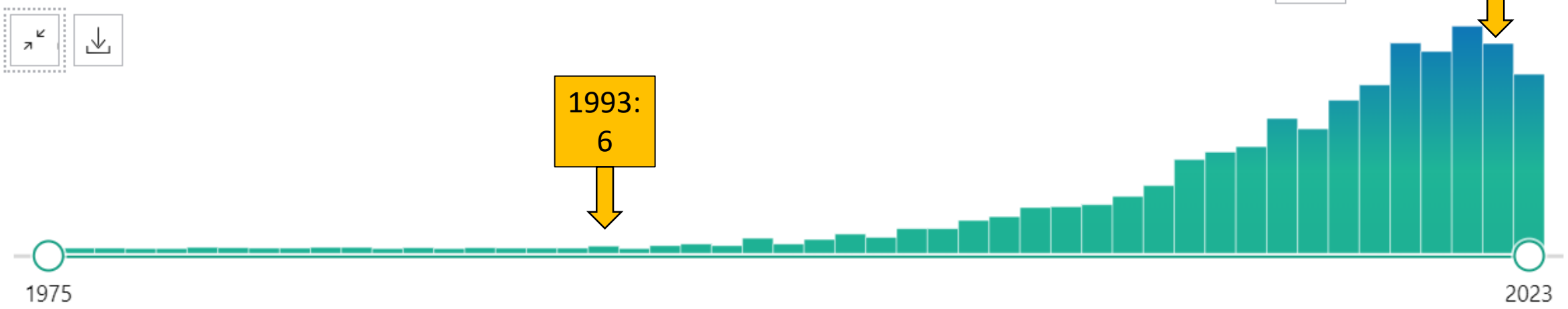
User Guide

Save Email Send to Sort by: Most recent Display options

RESULTS BY YEAR

4,432 results

Page 1 of 23



National Library of Medicine
National Center for Biotechnology Information

Log in

PubMed®

early intervention AND mental health

Search

Advanced Create alert Create RSS

User Guide

Save Email Send to Sort by: Most recent Display op

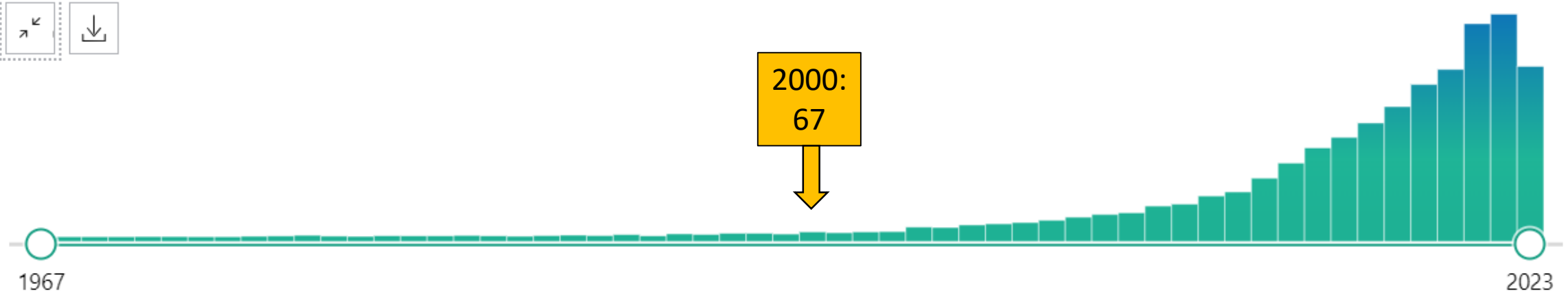
RESULTS BY YEAR

10,776 results

Page 1 of 54

2022: 1550

2000: 67



PLAN

- INTRODUCTION: Achievements of early intervention
- LIMITATIONS AND SOME WAYS FORWARD: Overcoming hurdles and challenges
  - Clinical domain
  - Neurobiological mechanisms
  - Political issues
  - Societal challenges
- CONCLUSIONS

PLAN

- INTRODUCTION: Achievements of early intervention
- LIMITATIONS AND SOME WAYS FORWARD: Overcoming hurdles and challenges
  - Clinical domain
  - Neurobiological mechanisms
  - Political issues
  - Societal challenges
- CONCLUSIONS

Clinical challenges

Improving early intervention in psychosis

REVIEW

CURRENT OPINION

How successful are first episode programs? A review of the evidence for specialized assertive early intervention

Merete Nordentoft, Jesper Østrup Rasmussen, Marianne Melau, Carsten R. Hjorthøj, and Anne A.E. Thorup

- Compared to standard care, specialized programs are more effective in
  - dealing with negative symptoms
  - lead to greater reduction in substance abuse
  - reduce use of hospital beds
  - improve patient satisfaction
  - are less costly
- **If the duration of the program is too short, these benefits are unfortunately not maintained when patients return to regular care.**
- **2-year programs are too short, but the ideal duration has yet to be defined**

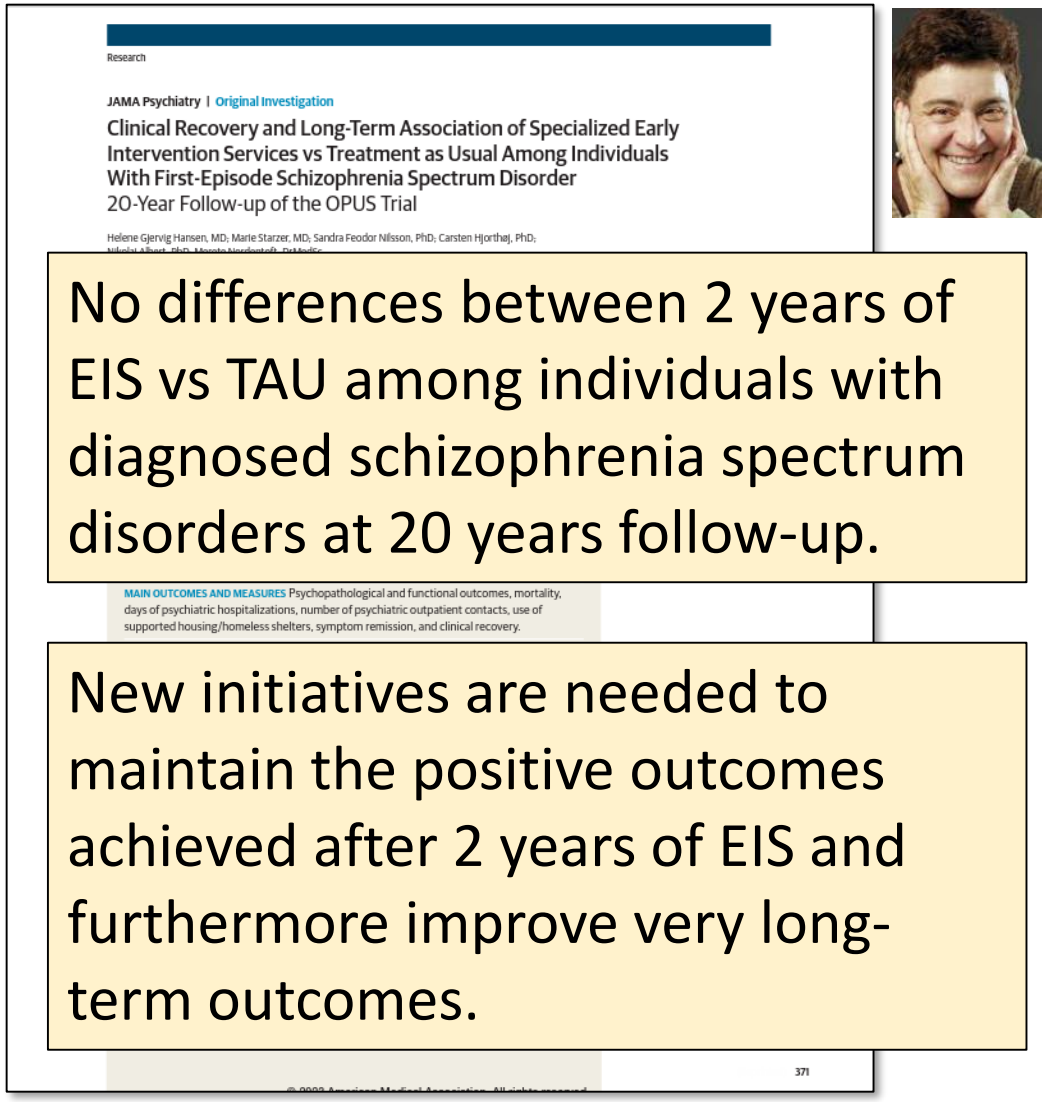
INTRODUCTI

The illness pr
disorders appe
and early in its
the rationale fo
qualified inter
possible. The
long periods o
with the highe
of contact with
[2–4], develop
criminality [5-
person and his
sion of the imp
and their know
manage it may
[8], which lea
[9,10].

0951-7367 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins www.co-psychiatry.com

Curr Opin Psychiatry 2014, 27:167–172

Limitations of early intervention in psychosis



Research

JAMA Psychiatry | Original Investigation

Clinical Recovery and Long-Term Association of Specialized Early Intervention Services vs Treatment as Usual Among Individuals With First-Episode Schizophrenia Spectrum Disorder
20-Year Follow-up of the OPUS Trial

Helene Gjervig Hansen, MD; Marie Starzer, MD; Sandra Feodor Nilsson, PhD; Carsten Hjorthøj, PhD;

MAIN OUTCOMES AND MEASURES Psychopathological and functional outcomes, mortality, days of psychiatric hospitalizations, number of psychiatric outpatient contacts, use of supported housing/homeless shelters, symptom remission, and clinical recovery.

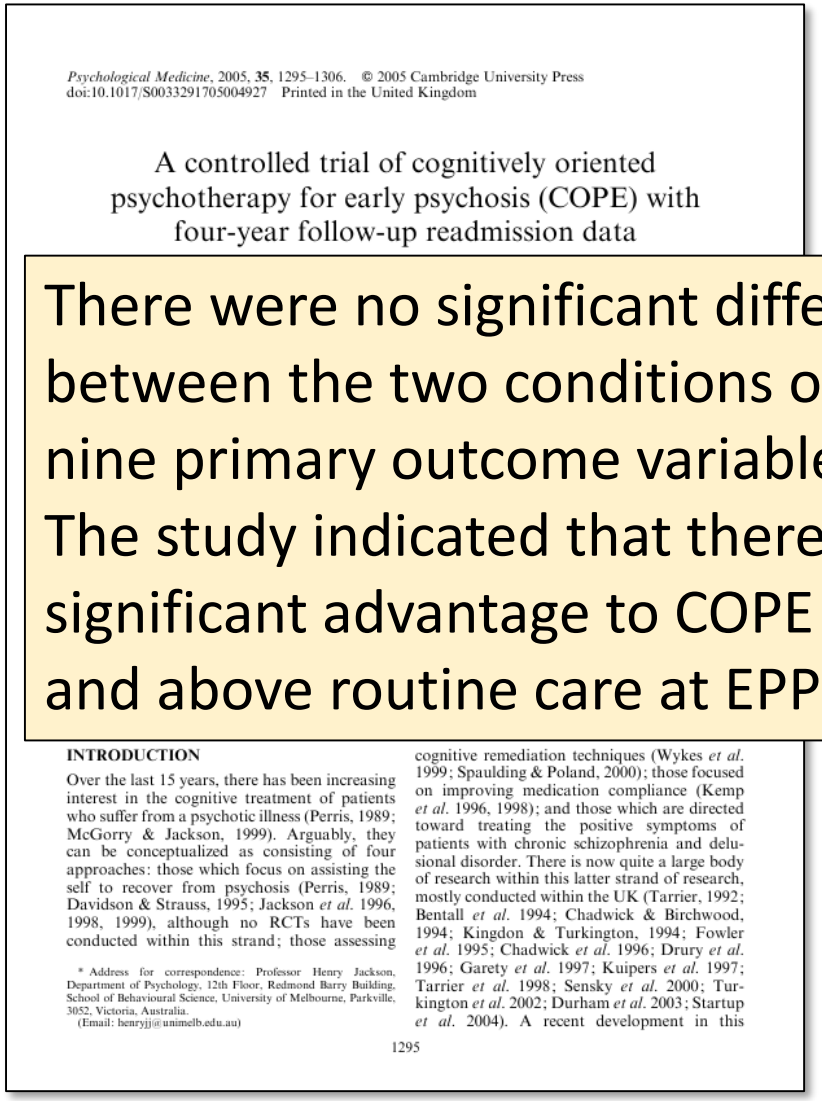
371

No differences between 2 years of EIS vs TAU among individuals with diagnosed schizophrenia spectrum disorders at 20 years follow-up.

New initiatives are needed to maintain the positive outcomes achieved after 2 years of EIS and furthermore improve very long-term outcomes.

- **Absence of long term efficacy**
- **Problem:** The poor quality of treatment after FEP tretament
- **Future developments:**
- Higher qualtiy of the entire treatement for mental health issues, event after FEP specialized treatment

Limitations of early intervention in psychosis



Psychological Medicine, 2005, **35**, 1295–1306. © 2005 Cambridge University Press
doi:10.1017/S0033291705004927 Printed in the United Kingdom

A controlled trial of cognitively oriented psychotherapy for early psychosis (COPE) with four-year follow-up readmission data

There were no significant differences between the two conditions on the nine primary outcome variables.
The study indicated that there was no significant advantage to COPE over and above routine care at EPPIC.

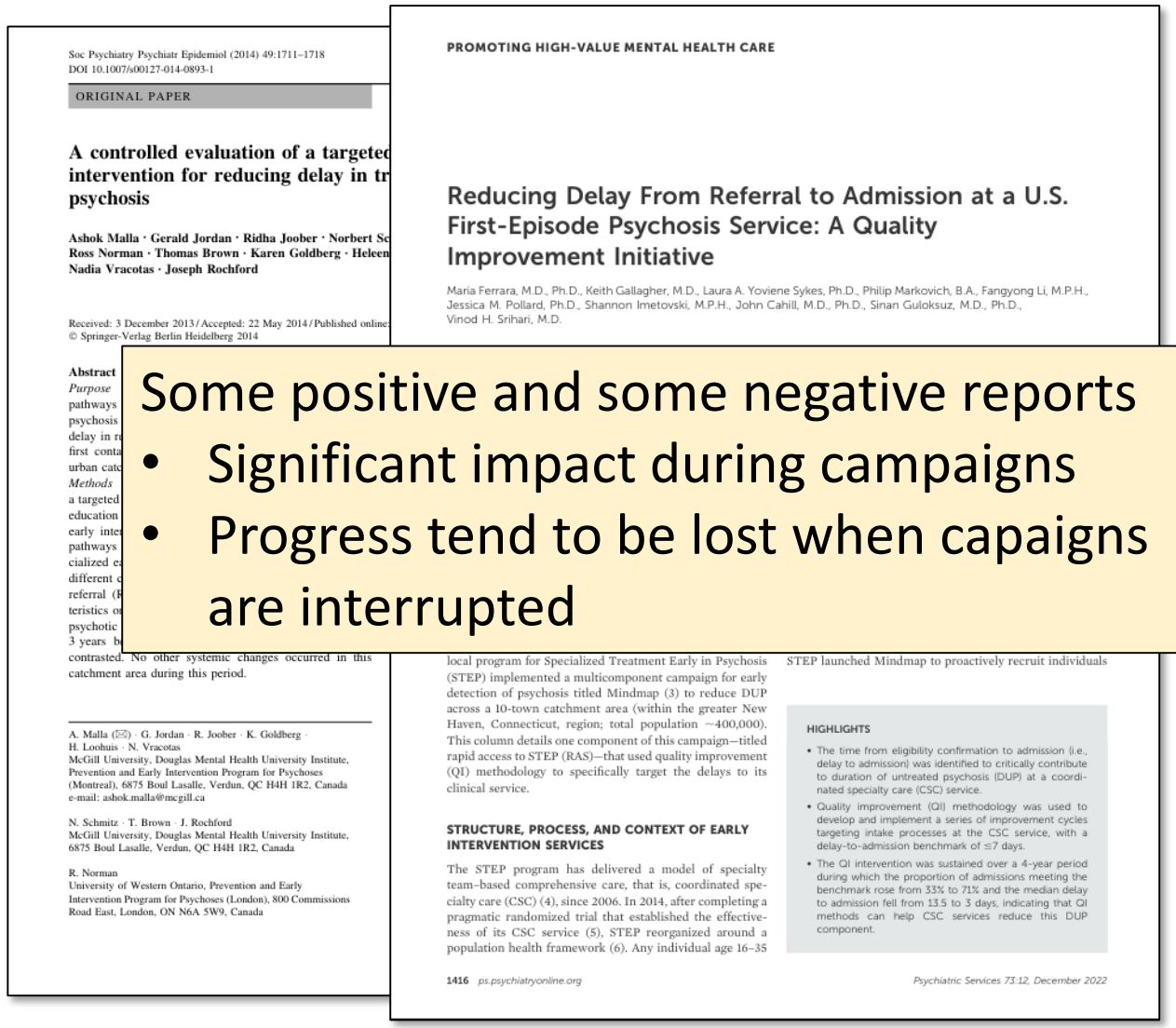
INTRODUCTION

Over the last 15 years, there has been increasing interest in the cognitive treatment of patients who suffer from a psychotic illness (Perris, 1989; McGorry & Jackson, 1999). Arguably, they can be conceptualized as consisting of four approaches: those which focus on assisting the self to recover from psychosis (Perris, 1989; Davidson & Strauss, 1995; Jackson *et al.* 1996, 1998, 1999), although no RCTs have been conducted within this strand; those assessing cognitive remediation techniques (Wykes *et al.* 1999; Spaulding & Poland, 2000); those focused on improving medication compliance (Kemp *et al.* 1996, 1998); and those which are directed toward treating the positive symptoms of patients with chronic schizophrenia and delusional disorder. There is now quite a large body of research within this latter strand of research, mostly conducted within the UK (Tarrier, 1992; Bentall *et al.* 1994; Chadwick & Birchwood, 1994; Kingdon & Turkington, 1994; Fowler *et al.* 1995; Chadwick *et al.* 1996; Drury *et al.* 1996; Garety *et al.* 1997; Kuipers *et al.* 1997; Tarrier *et al.* 1998; Sensky *et al.* 2000; Turkington *et al.* 2002; Durham *et al.* 2003; Startup *et al.* 2004). A recent development in this

* Address for correspondence: Professor Henry Jackson, Department of Psychology, 12th Floor, Redmond Barry Building, School of Behavioural Science, University of Melbourne, Parkville, 3052, Victoria, Australia.
(Email: henryjj@unimelb.edu.au)

- **Difficulties to demonstrate the superiority of specific psychological interventions**
- **May mean that other elements of early intervention programs are more critical**:
  - psychotherapy itself
  - engagement
  - continuity of care
  - optimism
- **Future**:
  - Keep developing new approaches
  - Train psychiatrists in psychotherapy
  - Digital approach

Limitations of early intervention in psychosis



Soc Psychiatry Psychiatr Epidemiol (2014) 49:1711–1718
DOI 10.1007/s00127-014-0893-1

ORIGINAL PAPER

A controlled evaluation of a targeted intervention for reducing delay in tr psychosis

Ashok Malla · Gerald Jordan · Ridha Joober · Norbert Sc Ross Norman · Thomas Brown · Karen Goldberg · Heleen Nadia Vracotas · Joseph Rochford

Received: 3 December 2013 / Accepted: 22 May 2014 / Published online:
© Springer-Verlag Berlin Heidelberg 2014

Abstract
Purpose
pathways
psychosis
delay in r
first conta
urban cat
Methods
a targeted
education
early inte
pathways
cialized e
different c
referral (R
teristics o
psychotic
3 years b
contrasted. No other systemic changes occurred in this catchment area during this period.

A. Malla (✉) · G. Jordan · R. Joober · K. Goldberg · H. Loohuis · N. Vracotas
McGill University, Douglas Mental Health University Institute, Prevention and Early Intervention Program for Psychoses (Montreal), 6875 Boul Lasalle, Verdun, QC H4H 1R2, Canada
e-mail: ashok.malla@mcgill.ca

N. Schmitz · T. Brown · J. Rochford
McGill University, Douglas Mental Health University Institute, 6875 Boul Lasalle, Verdun, QC H4H 1R2, Canada

R. Norman
University of Western Ontario, Prevention and Early Intervention Program for Psychoses (London), 800 Commissions Road East, London, ON N6A 5W9, Canada

PROMOTING HIGH-VALUE MENTAL HEALTH CARE

Reducing Delay From Referral to Admission at a U.S. First-Episode Psychosis Service: A Quality Improvement Initiative

Maria Ferrara, M.D., Ph.D., Keith Gallagher, M.D., Laura A. Yoviene Sykes, Ph.D., Philip Markovich, B.A., Fangyong Li, M.P.H., Jessica M. Pollard, Ph.D., Shannon Imetovski, M.P.H., John Cahill, M.D., Ph.D., Sinan Guloksuz, M.D., Ph.D., Vinod H. Srihari, M.D.

local program for Specialized Treatment Early in Psychosis (STEP) implemented a multicomponent campaign for early detection of psychosis titled Mindmap (3) to reduce DUP across a 10-town catchment area (within the greater New Haven, Connecticut, region; total population ~400,000). This column details one component of this campaign—titled rapid access to STEP (RAS)—that used quality improvement (QI) methodology to specifically target the delays to its clinical service.

STRUCTURE, PROCESS, AND CONTEXT OF EARLY INTERVENTION SERVICES

The STEP program has delivered a model of specialty team–based comprehensive care, that is, coordinated specialty care (CSC) (4), since 2006. In 2014, after completing a pragmatic randomized trial that established the effectiveness of its CSC service (5), STEP reorganized around a population health framework (6). Any individual age 16–35

STEP launched Mindmap to proactively recruit individuals

HIGHLIGHTS

- The time from eligibility confirmation to admission (i.e., delay to admission) was identified to critically contribute to duration of untreated psychosis (DUP) at a coordinated specialty care (CSC) service.
- Quality improvement (QI) methodology was used to develop and implement a series of improvement cycles targeting intake processes at the CSC service, with a delay-to-admission benchmark of ≤7 days.
- The QI intervention was sustained over a 4-year period during which the proportion of admissions meeting the benchmark rose from 33% to 71% and the median delay to admission fell from 13.5 to 3 days, indicating that QI methods can help CSC services reduce this DUP component.

1416 ps.psychiatryonline.org

Psychiatric Services 73:12, December 2022

Some positive and some negative reports

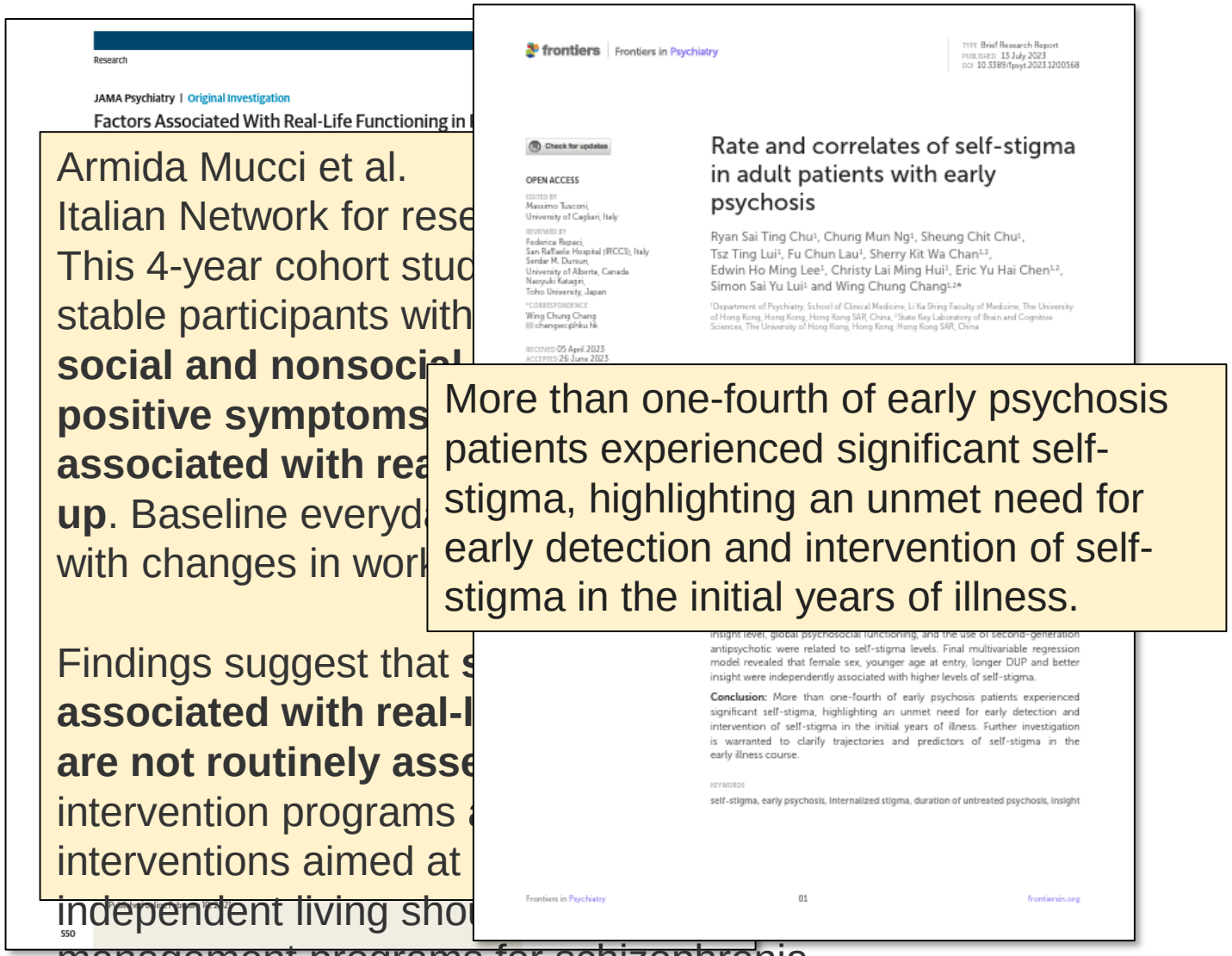
- Significant impact during campaigns
- Progress tend to be lost when capaigns are interrupted

- **Reducing DUP remains a challenge**
- Most patients continue to come from emergency departments

- **Problem:**
  - Stigma and
  - lack of mental heatlh litteracy

- **Future:**
  - Promote mental health litteracy in the population and schools
  - Mental health as capital to protect

Limitations of early intervention in psychosis


Research

JAMA Psychiatry | Original Investigation

Factors Associated With Real-Life Functioning in

Armida Mucci et al.
Italian Network for rese
This 4-year cohort stud
stable participants with
social and nonsocial
positive symptoms
associated with rea
up. Baseline everyd
with changes in work

Findings suggest that **s**
associated with real-l
are not routinely asse
intervention programs
interventions aimed at
independent living sho
management programs for schizophrenia.

550

frontiers | Frontiers in Psychiatry

TYPE Brief Research Report
PUBLISHED 13 July 2023
DOI 10.3389/fpsyt.2023.1200568

Check for updates

OPEN ACCESS

EDITED BY
Massimo Tusconi,
University of Cagliari, Italy

REVIEWED BY
Federica Repaci,
San Raffaele Hospital (IRCCS), Italy
Serdar M. Dursun,
University of Alberta, Canada
Naoyuki Katagiri,
Toho University, Japan

*CORRESPONDENCE
Wing Chung Chang
wingchangac@hku.hk

RECEIVED 05 April 2023
ACCEPTED 26 June 2023

Rate and correlates of self-stigma in adult patients with early psychosis

Ryan Sai Ting Chu[1], Chung Mun Ng[1], Sheung Chit Chu[1], Tsz Ting Lui[1], Fu Chun Lau[1], Sherry Kit Wa Chan[1,2], Edwin Ho Ming Lee[1], Christy Lai Ming Hui[1], Eric Yu Hai Chen[1,2], Simon Sai Yu Lui[1] and Wing Chung Chang[1,2]*

[1]Department of Psychiatry, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, Hong Kong SAR, China, [2]State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong, Hong Kong SAR, China

More than one-fourth of early psychosis patients experienced significant self-stigma, highlighting an unmet need for early detection and intervention of self-stigma in the initial years of illness.

insight level, global psychosocial functioning, and the use of second-generation antipsychotic were related to self-stigma levels. Final multivariable regression model revealed that female sex, younger age at entry, longer DUP and better insight were independently associated with higher levels of self-stigma.

Conclusion: More than one-fourth of early psychosis patients experienced significant self-stigma, highlighting an unmet need for early detection and intervention of self-stigma in the initial years of illness. Further investigation is warranted to clarify trajectories and predictors of self-stigma in the early illness course.

KEYWORDS

self-stigma, early psychosis, internalized stigma, duration of untreated psychosis, insight

Frontiers in Psychiatry 01 frontiersin.org

- **Rate of functional recovery- remains low**
- **Problem :** Linked to
  - various elements that are not assessed or treated
  - self-stigma
  - Lack of adaptation of our society to people with difficulties
- **Adapt society to the needs of patients**

Expanding early intervention to other disorders

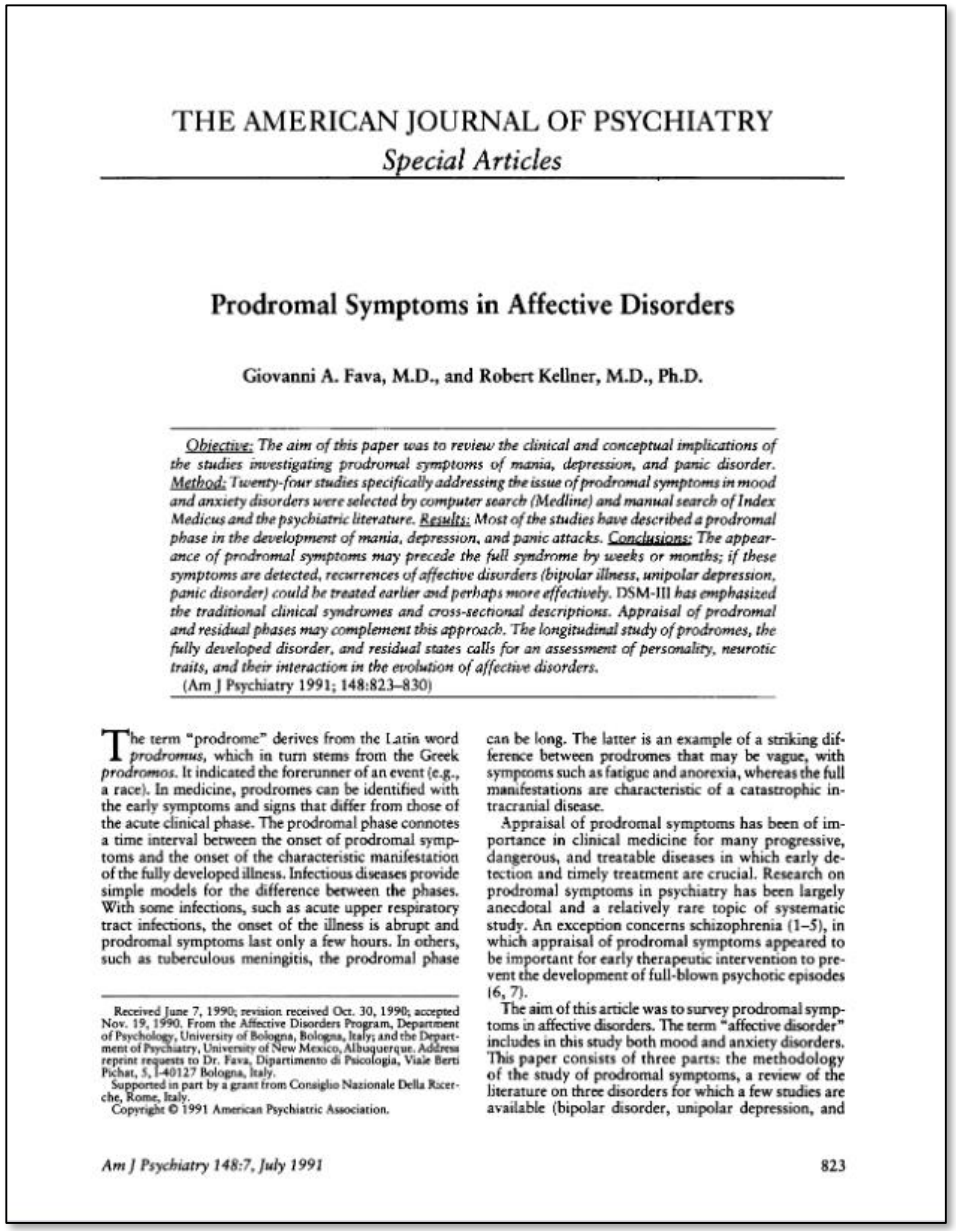
Early intervention in other diagnoses?

- Majority of developments and progress in psychosis
- Limited progress in other disorders
  - Exceptions: Autism, personality disorders, …
- Potential causes:
  - Lack of interest or investment in some domains
  - Different concepts of the disorder: classification in silos and sub-groups rather than along time
  - Difficulties in identifying relevant targets
  - Complexity of the onset: bipolar disorder

The exemple of bipolar disorder

The pioneers

- Fava & Kellner: *AJP 1991: « The appearance of* ***prodromal symptoms may precede the full syndrome by weeks or months; if these symptoms are detected****, recurrences of affective disorders (bipolar illness, unipolar depression, panic disorder)* ***could be treated earlier and perhaps more effectively****.»*



THE AMERICAN JOURNAL OF PSYCHIATRY
Special Articles

Prodromal Symptoms in Affective Disorders

Giovanni A. Fava, M.D., and Robert Kellner, M.D., Ph.D.

Objective: The aim of this paper was to review the clinical and conceptual implications of the studies investigating prodromal symptoms of mania, depression, and panic disorder. *Method:* Twenty-four studies specifically addressing the issue of prodromal symptoms in mood and anxiety disorders were selected by computer search (Medline) and manual search of Index Medicus and the psychiatric literature. *Results:* Most of the studies have described a prodromal phase in the development of mania, depression, and panic attacks. *Conclusions:* The appearance of prodromal symptoms may precede the full syndrome by weeks or months; if these symptoms are detected, recurrences of affective disorders (bipolar illness, unipolar depression, panic disorder) could be treated earlier and perhaps more effectively. DSM-III has emphasized the traditional clinical syndromes and cross-sectional descriptions. Appraisal of prodromal and residual phases may complement this approach. The longitudinal study of prodromes, the fully developed disorder, and residual states calls for an assessment of personality, neurotic traits, and their interaction in the evolution of affective disorders.
(Am J Psychiatry 1991; 148:823–830)

The term "prodrome" derives from the Latin word *prodromus*, which in turn stems from the Greek *prodromos*. It indicated the forerunner of an event (e.g., a race). In medicine, prodromes can be identified with the early symptoms and signs that differ from those of the acute clinical phase. The prodromal phase connotes a time interval between the onset of prodromal symptoms and the onset of the characteristic manifestation of the fully developed illness. Infectious diseases provide simple models for the difference between the phases. With some infections, such as acute upper respiratory tract infections, the onset of the illness is abrupt and prodromal symptoms last only a few hours. In others, such as tuberculous meningitis, the prodromal phase can be long. The latter is an example of a striking difference between prodromes that may be vague, with symptoms such as fatigue and anorexia, whereas the full manifestations are characteristic of a catastrophic intracranial disease.

Appraisal of prodromal symptoms has been of importance in clinical medicine for many progressive, dangerous, and treatable diseases in which early detection and timely treatment are crucial. Research on prodromal symptoms in psychiatry has been largely anecdotal and a relatively rare topic of systematic study. An exception concerns schizophrenia (1–5), in which appraisal of prodromal symptoms appeared to be important for early therapeutic intervention to prevent the development of full-blown psychotic episodes (6, 7).

The aim of this article was to survey prodromal symptoms in affective disorders. The term "affective disorder" includes in this study both mood and anxiety disorders. This paper consists of three parts: the methodology of the study of prodromal symptoms, a review of the literature on three disorders for which a few studies are available (bipolar disorder, unipolar depression, and

Received June 7, 1990; revision received Oct. 30, 1990; accepted Nov. 19, 1990. From the Affective Disorders Program, Department of Psychology, University of Bologna, Bologna, Italy; and the Department of Psychiatry, University of New Mexico, Albuquerque. Address reprint requests to Dr. Fava, Dipartimento di Psicologia, Viale Berti Pichat, 5, I-40127 Bologna, Italy.
Supported in part by a grant from Consiglio Nazionale Della Ricerche, Rome, Italy.

First-episode mania: a neglected priority for early intervention

Philippe Conus, Patrick D. McGorry

Objective: While first-episode (FE) psychosis has become an important field of research, FE affective psychoses, and mania in particular, have been relatively neglected. This paper summarizes current knowledge about FE mania and explores the potential for early intervention.
Method: The main computerized psychiatric literature databases were accessed.
Results: When functional as well as symptomatic variables are considered, the outcome of mania is not as good as was formerly believed, a characteristic which is already present from the first episode. Various factors (lower socio-economic status, younger age at onset of illness, poor adherence to treatment, presence of comorbidity) have been identified as possible predictors of poor outcome. The prognostic value of the presence of psychotic symptoms and their congruence to mood, as well as the diagnostic subgroup, is less well established. This literature review also reveals striking similarities between manic and schizophreniform first episodes. Poor functional outcome in a significant proportion of patients following the first episode, high risk of suicide, high prevalence of comorbid diagnoses, worse outcome with a younger age at onset and with longer delay until treatment is initiated, and finally early presence of neuro-anatomical changes, are observed in both syndromes.
Conclusions: This pattern justifies the development of early intervention strategies for FE manic patients and supports more exploratory research to identify prodromal symptoms, which might ultimately lead to even earlier focus on preventive interventions.
Key words: early intervention, first-episode, mania, outcome, psychosis.

Australian and New Zealand Journal of Psychiatry 2002; 36:158–172

In recent years, the early phase of psychosis has become an important field of research in psychiatry, and the therapeutic strategies which were developed as a consequence of this growing interest may be beginning to improve the outcome in these potentially disastrous conditions [1]. Probably partly in reaction to the pessimism with which it was considered, schizophrenia has drawn most of the attention in this domain, to the point that 'early psychosis' is often equated to 'early schizophrenia'. As a consequence, first-episode (FE) affective psychoses have been relatively neglected. Mania in particular has been understudied, and the literature about FE mania is sparse. For many reasons, it is imperative that a preventive approach should be extended to the full range of FE psychosis.

First, mania is a frequent disorder, its lifetime prevalence in the USA being 1.6% [2]. Second, while the Kraepelinian view of mental illness was excessively pessimistic regarding schizophrenia, it has been excessively optimistic regarding manic-depression [3–6]. Third, many studies have shown that the number of manic episodes is a predictive factor for greater risk of relapse [7], more severe cognitive deficits [8–11] and worse overall outcome [5]. Besides the disruptive effect mood symptoms have on patient lives, up to 15% of patients can be expected to commit suicide without sustained therapy [12]. As expressed by K. Jamison [13]: '[This]

Philippe Conus, (Correspondence); Patrick D. McGorry
Early Psychosis Prevention and Intervention Centre, Locked Bag 10, Parkville, Victoria 3052, Australia.
Email: conusmichaelis@bigpond.com
Received 6 June 2001; revised 21 August 2001; accepted 28 August 2001.

Journal of Affective Disorders 257 (2019) 669–677

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Review article

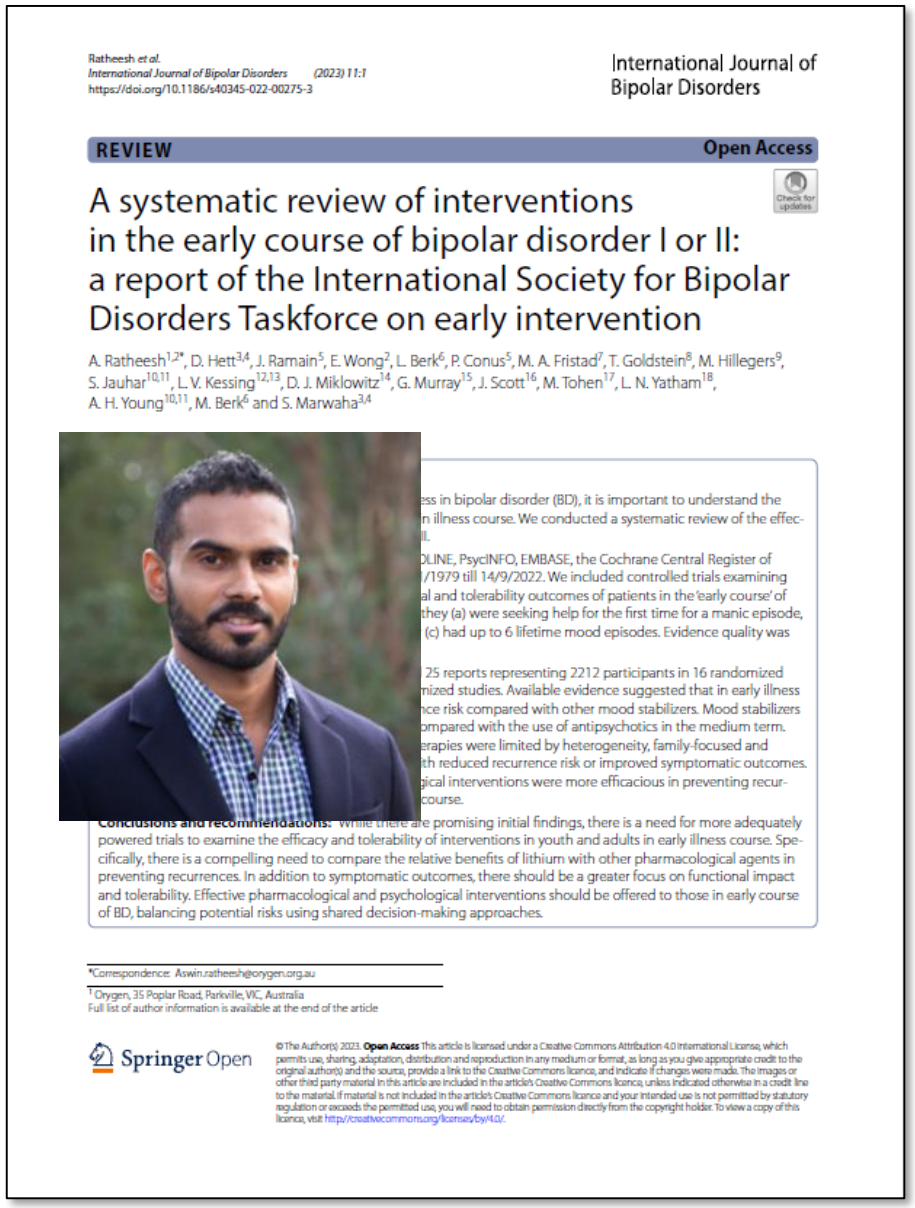
Early intervention for bipolar disorder – Do current treatment guidelines provide recommendations for the early stages of the disorder?

Chia Ming Fang[a,c], Sue Cotton[a,b], Kate Filia[a,b], Mark Phelan[d], Philippe Conus[e], Sameer Jauhar[f], Steven Marwaha[g], Patrick D McGorry[a,b], Christopher Davey[a,b,d], Michael Berk[a,b,h,i], Aswin Ratheesh[a,b,d,*]

Conclusions: There is a lack of emphasis on early BD among widely-respected current clinical guidelines, likely reflecting the dearth of primary data. Future evidence or consensus-based recommendations could significantly inform clinical practice for this population.

* Corresponding author at: Orygen, The National Centre of Excellence in Youth Mental Health, 35 Poplar Road, Parkville, Australia.
E-mail address: aswin.ratheesh@orygen.org.au (A. Ratheesh).

https://doi.org/10.1016/j.jad.2019.07.062
Received 8 March 2019; Received in revised form 3 July 2019; Accepted 29 July 2019
Available online 30 July 2019



Ratheesh et al.
International Journal of Bipolar Disorders (2023) 11:1
https://doi.org/10.1186/s40345-022-00275-3

International Journal of Bipolar Disorders

REVIEW Open Access

A systematic review of interventions in the early course of bipolar disorder I or II: a report of the International Society for Bipolar Disorders Taskforce on early intervention

A. Ratheesh[1,2*], D. Hett[3,4], J. Ramain[5], E. Wong[2], L. Berk[6], P. Conus[5], M. A. Fristad[7], T. Goldstein[8], M. Hillegers[9], S. Jauhar[10,11], L. V. Kessing[12,13], D. J. Miklowitz[14], G. Murray[15], J. Scott[16], M. Tohen[17], L. N. Yatham[18], A. H. Young[10,11], M. Berk[6] and S. Marwaha[3,4]

...ss in bipolar disorder (BD), it is important to understand the ...n illness course. We conducted a systematic review of the effec-...ll.

...DLINE, PsycINFO, EMBASE, the Cochrane Central Register of .../1979 till 14/9/2022. We included controlled trials examining ...al and tolerability outcomes of patients in the 'early course' of ...they (a) were seeking help for the first time for a manic episode, ...(c) had up to 6 lifetime mood episodes. Evidence quality was ...

...25 reports representing 2212 participants in 16 randomized ...mized studies. Available evidence suggested that in early illness ...nce risk compared with other mood stabilizers. Mood stabilizers ...ompared with the use of antipsychotics in the medium term. ...erapies were limited by heterogeneity, family-focused and ...th reduced recurrence risk or improved symptomatic outcomes. ...gical interventions were more efficacious in preventing recur-...course.

Conclusions and recommendations: While there are promising initial findings, there is a need for more adequately powered trials to examine the efficacy and tolerability of interventions in youth and adults in early illness course. Specifically, there is a compelling need to compare the relative benefits of lithium with other pharmacological agents in preventing recurrences. In addition to symptomatic outcomes, there should be a greater focus on functional impact and tolerability. Effective pharmacological and psychological interventions should be offered to those in early course of BD, balancing potential risks using shared decision-making approaches.

*Correspondence: Aswin.ratheesh@orygen.org.au
[1] Orygen, 35 Poplar Road, Parkville, VIC, Australia
Full list of author information is available at the end of the article

Systematic review of the effectiveness of interventions in the early course of BD I or II.

Only 25 studies between 1971 and 2022: 16 randomized studies and 9 non-randomized studies

Main findings in the early phase of BD:

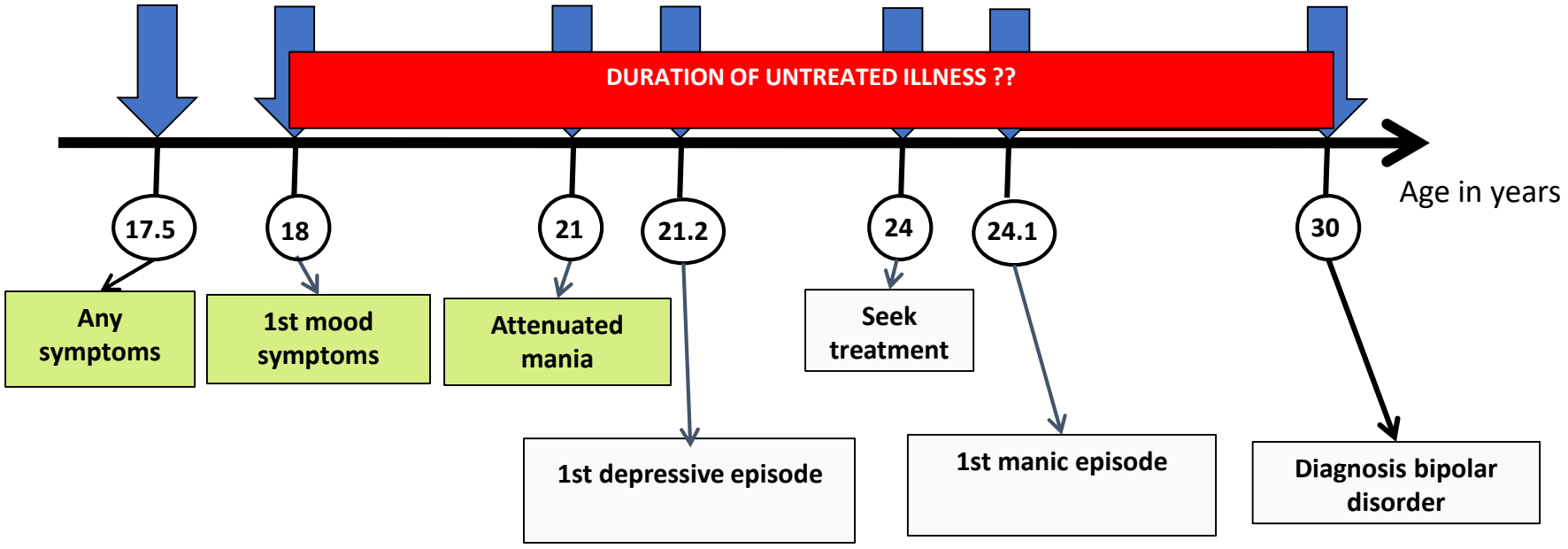
- **Lithium:** lower recurrence risk than other mood stabilizers.
- **Mood stabilizers** associated with better global functioning than antipsychotics in the medium term
- **Psychological therapies**:
  - few data limited by heterogeneity
  - family-focused and CBT associated with reduced recurrence risk or improved symptomatic outcomes.

- **Same pharmacological interventions were more efficacious** in preventing recurrences when utilized in earlier illness course.

DO WE NEED EARLY INTERVENTION IN BIPOLAR DISORDERS?

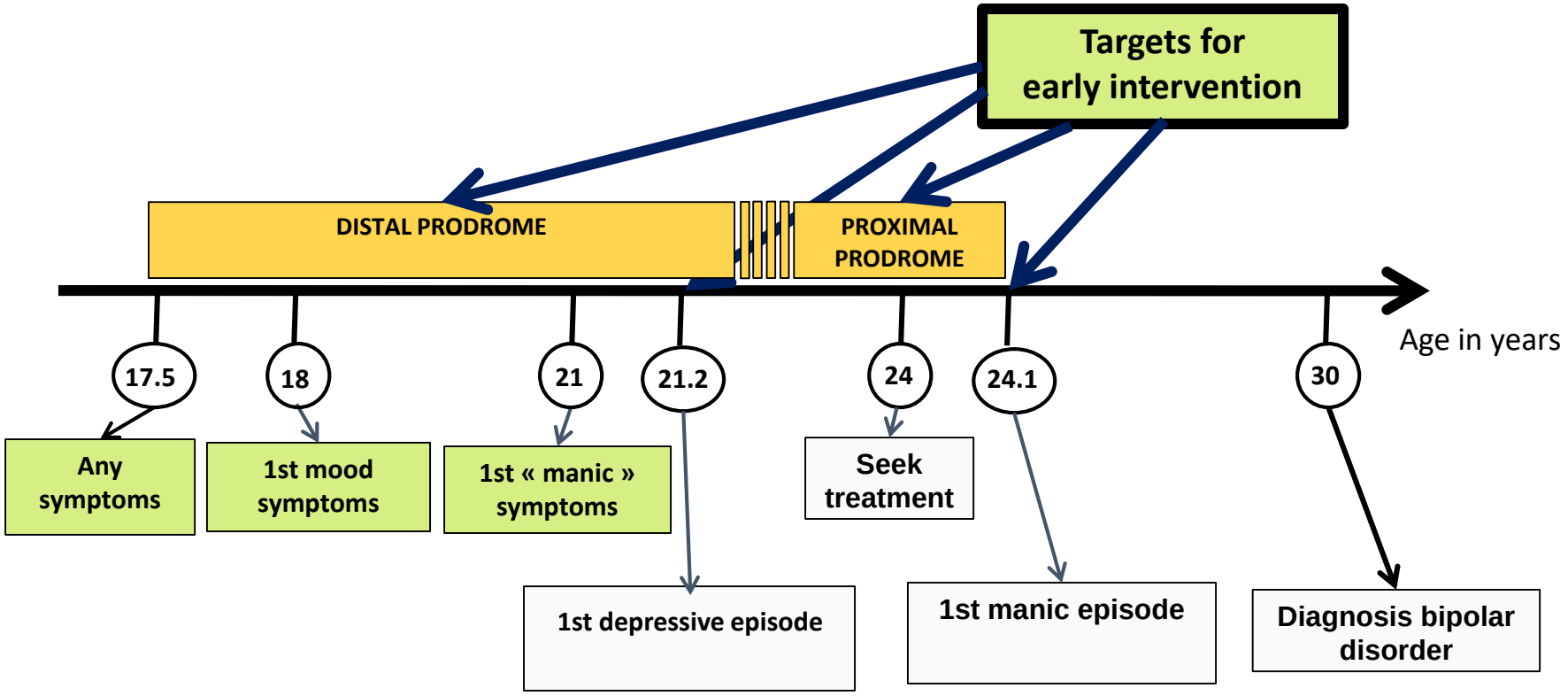
- **Poor outcome,** already after first episode mania
  - ***Rapid syndromal recovery*** *from first manic episode (90%), BUT*
  - ***Persistence of symptoms*** *(anxiety, depression: 40%)*
  - ***Poor functional outcome*** *(60% fail to return to premorbid level) (Conus et al., 2004)*
- **Long treatment delay** : 6 -10 years between first mania and diagnosis of BD *(Post 2003; Baethge 2003)*
- **Lack of specific treatment guidelines,** despite stage specific needs
- Suggestion of an **active and progressive process** *(Berk et al, 2011)*
  - *Decrease in response to treatment with number of episodes*
  - *Increase in relapse risk with number of episodes*

Development stages of bipolar disorder



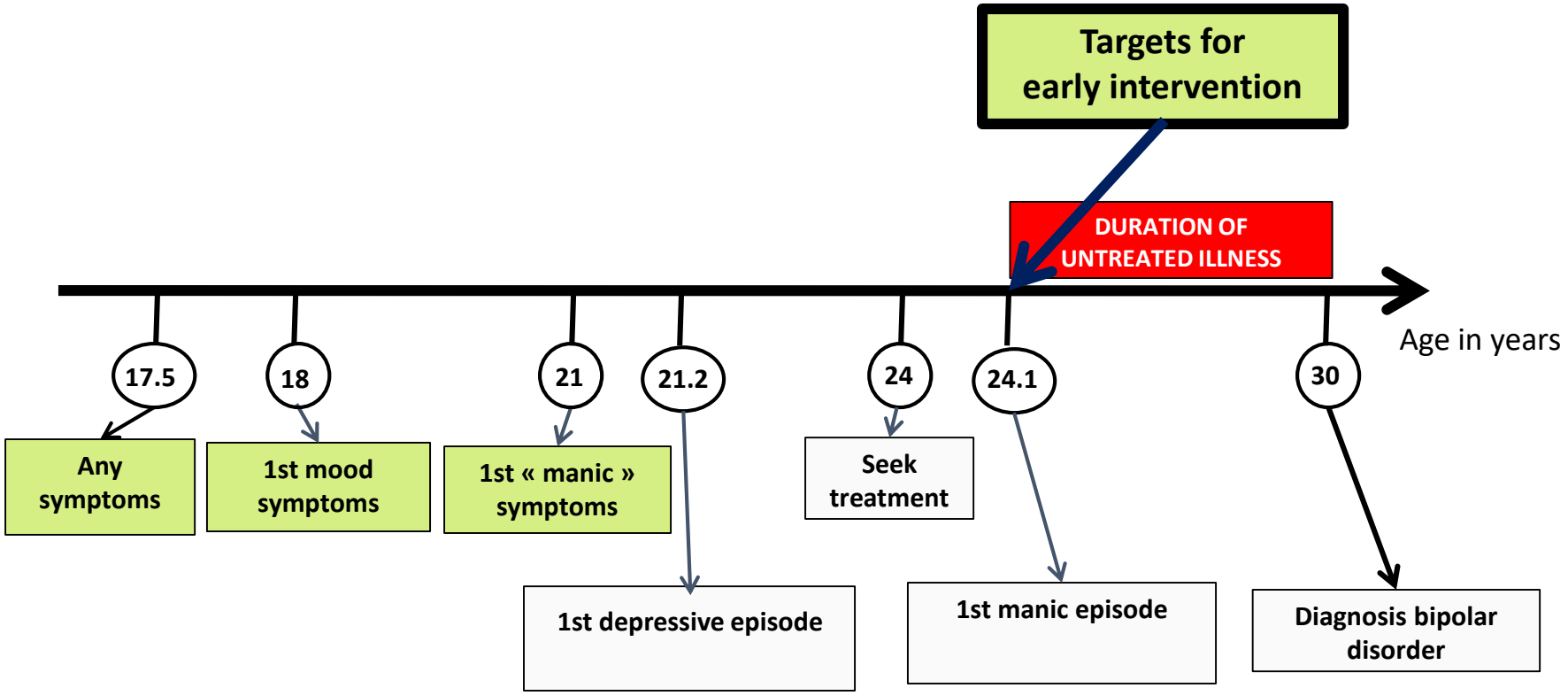
Adapted from Berk et al. 2007

Defining targets for early intervention in bipolar disorder



Conus P, 2022

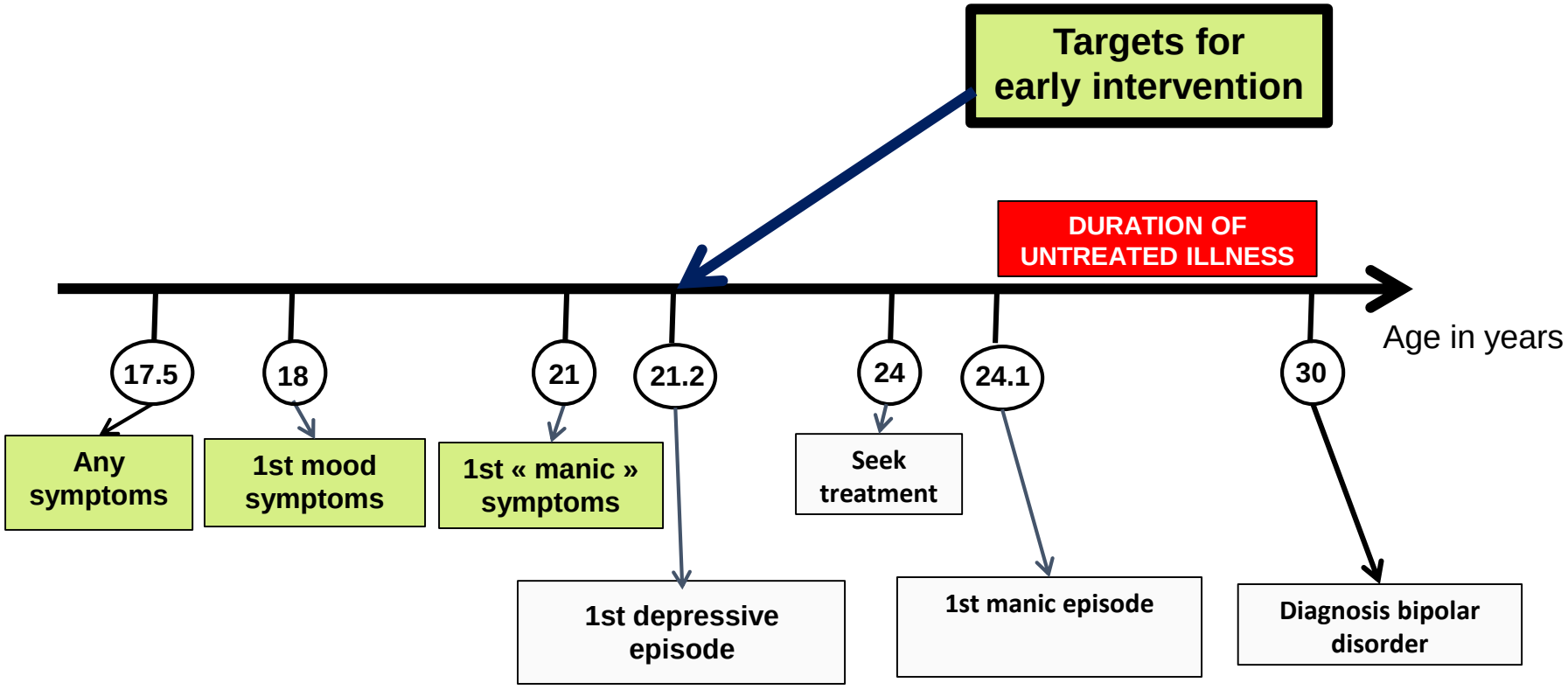
Improving detection of first epsiode mania



Improving detection of first epsiode mania

- **Promote better knowledge of mania in young patients**
  - **Manic state are often atypical in young people**
    - Irritability, increased energy, flight of ideas rather than euphoria
    - Should not be mistaken ith behavioural problems
  - **Psychotic symptoms are commonly present**
    - Clinicians should not be blinded by this aspect of presentation
    - There are no clearly discriminant psychotic symptoms
  - **High rate of substance abuse**
    - Beware of misdiagnosis with SUD or personnality disorder
  - **Keep diagnosis open if there is doubt**
    - dimensional diagnosis is more adapted to early phase of psychiatric disorders

Identifying bipolar depression

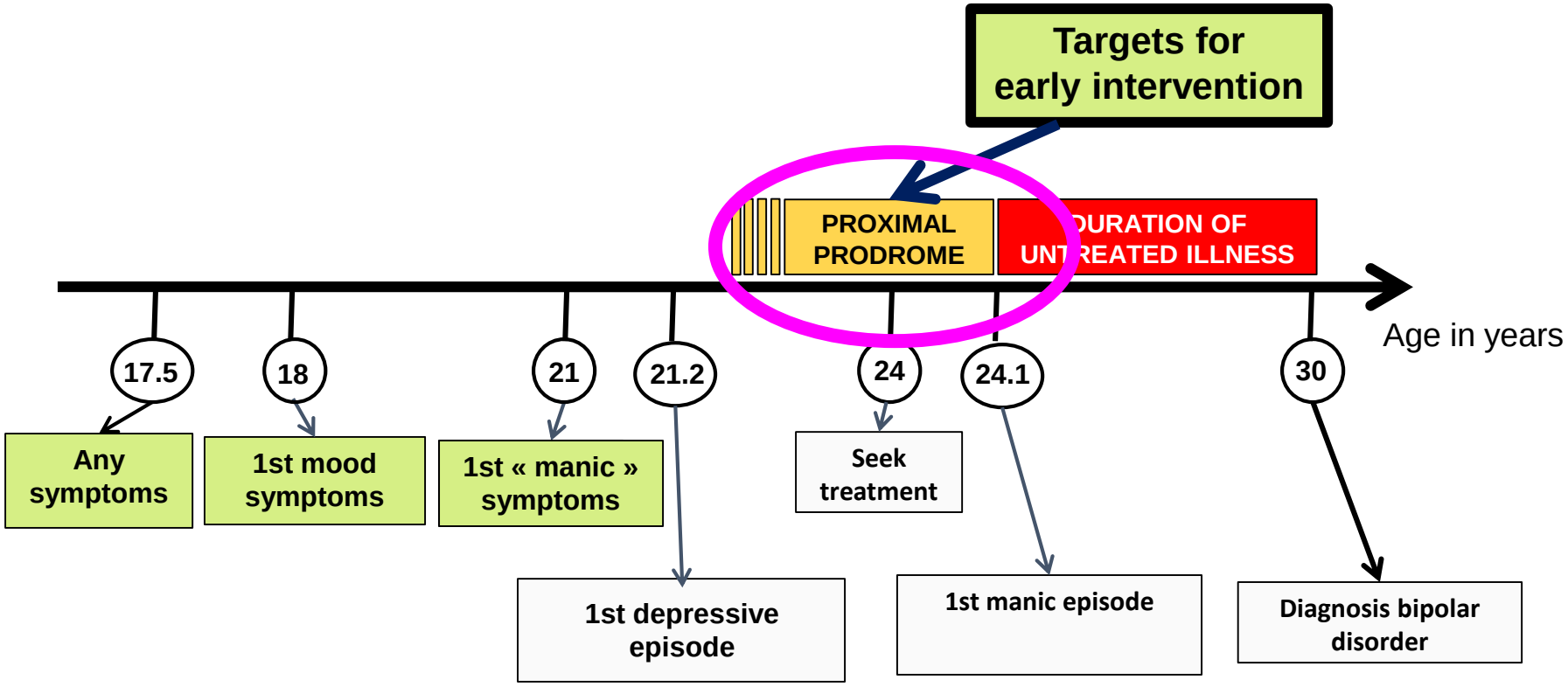


Identifying bipolar depression

- Depression is the most common initial manifestation of bipolar disorders *(Perugi 2000, Berk 2007)*
- Majority of the pathology is in the depressive phase (ratio 3 : 1 with mania)
- Prescription of antidepressants may lead to mania switch

- Currently limited knowledge regarding specific characteristics:
  - Berk et al 2004; literature review:
    - *Early onset,*
    - *Abrupt onset and off set,*
    - *Psychomotor retardation (alteration of emotional reactivity, delayed verbal answers, slowness of mouvements),*
    - *Melancholic symptoms,*
    - *Atypical depressive symptoms (hypersomnia, hyperphagia, lead paralysis)*
    - *Irritability, mixed states, mood lability, high rate of relapse*
  - Bipolar Depression Rating Scale *(Berk et al., 2007)*
  - *Need for validation study*

Identifying the proximal prodrome to first episode mania



ELSEVIER

The initial prod

Katherine N. Th
John

PACE Clinic, Mental Health

Received

Abstract

Background: The initial
available data only addressi
prodrome to bipolar affectiv
treatment at the Personal A
12-month period using stand
the end of the treatment p
mania developing at a later
Limitations: The generalisa
findings are likely to be inf
at risk of psychosis rather t
bipolar disorder, which has
clearly distinguished betwee
hope our prospective data
developing suitable prevent
© 2002 Elsevier B.V. All rig

Keywords: Bipolar affective dis

1. Introduction

Bipolar affective disor
cern (Kessler et al., 1994
mood symptoms associ

* Corresponding author. Te
9342-2941.
E-mail address: conusmicha

0165-0327/$ - see front matter
doi:10.1016/S0165-0327(02)001

Bipolar Disorders 2008: 10: 555–565

Review Article

The proximal p
mania – a new

Conus P, Ward J, Hallam KT, Luc
Berk M. The proximal prodrome to
for early intervention.
Bipolar Disord 2008: 10: 555–565.
compilation © 2008 Blackwell Mun

Objective: Affective psychoses and
neglected in the development of ear
aims to gather current knowledge o
in order to define new targets for e

Methods: Literature review based
(MEDLINE, PUBMED and PSYC
literature.

Results: Based on current knowled
aiming at the identification of impe
realistic and manageable strategy t
the period preceding the onset of t
through a prodromal phase marked
sleep disturbance, and other sympt
functional impairment. Additionall
vulnerability to bipolar disorders h

Conclusions: In the few months pr
go through a prodrome phase (pro
become an important target for earl
the low specificity of the symptoms
defining high-risk profiles to first-e
certain risk factors or markers of v
needed in high-risk groups (e.g., bi
conducted in first-episode mania c
information about this critical pha

In recent years, much clinical and
has been directed at the early a
phases of psychotic disorders (1).
the focus has been put almost exc
affective disorders, to the point tha
has often been equated to early s
As a result, research into the
affective psychoses, such as bipola
der (BPAD), has been a relativel

The authors of this paper do not have any c
that might pose a conflict of interest in conne
script.

ELSEVIER

Jo
journa

Brief report

Characterisation of the p
Results of a retrospective

Philippe Conus [a,b,c,*], Janine Wa
Michael Berk [c,d,e], Patrick D. Mc

[a] *Traitement et Intervention Précoce dans les troubles*
Clinique de Cery, 1008 Prilly, Switzerland
[b] *Early Psychosis Prevention and Intervention Centre*
[c] *Orygen Youth Health Research Centre, Centre for Yo*
[d] *Department of Clinical and Biomedical Sciences: Bar*
[e] *Mental Health Research Institute, Parkville, Australia*

ARTICLE INFO

Article history:
Received 5 June 2009
Received in revised form 27 December 2009
Accepted 28 December 2009
Available online 20 January 2010

Keywords:
Bipolar disorder
Prodrome
Psychosis
High risk
Early detection

1. Introduction

Affective psychoses have been neglect
ment of early intervention strategies (C
2002). Most knowledge on the onset
disorders (BPAD) is derived from stu
populations of bipolar off-spring (Lapalme e

* Corresponding author. Département de Psychiat
Lausanne, 1008 Prilly, Switzerland. Tel.: +41 21 643 61 1
E-mail address: philippe.conus@chuv.ch (P. Conu

0165-0327/$ – see front matter © 2010 Elsevier B.V

ELSEVIER

Jo
journ

Brief report

A preliminary evaluatio
disorders in help-seekin

Andreas Bechdolf *[,1,2], Barnaby
Jonathan Kettle, Phillippe Conu
Michael Berk, Patrick D. McGo

ORYGEN Youth Health, Department of Youth Mental

ARTICLE INFO

Article history:
Received 11 December 2009
Received in revised form 8 June 2010
Accepted 9 June 2010
Available online 8 July 2010

Keywords:
Prodrome
Mania
Bipolar disorder

1. Introduction

Clinicians and researchers have rece
intervening early in the course of bipola
(BPAD), in the prodromal phase, may r
and economic burden, as this strategy
delay, lessen the severity of, or even

* Corresponding author. ORYGEN Youth Health (
Road, 3052 Parkville, Victoria, Australia. Tel.: +61
93423106.
E-mail address: andreas.bechdolf@uk-koeln.de
[1] Department of Psychiatry, University of Melbo
[2] Department of Psychiatry and Psychotherapy,
Germany.

0165-0327/$ – see front matter © 2010 Elsevier B.
doi:10.1016/j.jad.2010.06.016

Bipolar Disorders 2014: 16: 493–504

Original Article

The predictive v
(prodromal) crit
adolescents and
study

Bechdolf A, Ratheesh A, Cotton SM,
Bingmann T, Yung AR, Berk M, McG
of bipolar at-risk (prodromal) criteria
young adults: a prospective study.
Bipolar Disord 2014: 16: 493–504. © 2
Published by John Wiley & Sons Ltd.

Objectives: There are no established to
for developing bipolar disorder. We de
criteria for bipolar disorder [bipolar at
the present
criteria.

Methods:
Orygen Yo
for young
Australia.
group of i
a period of
being in th
threshold
plus geneti
defined by
days, in lin

Results: A
eligible pa
participant
participant
up, five BA
hypomania
[$\chi^2(1) = 5.$
IV diagnos

Conclusion
persons pr
need furth
up periods

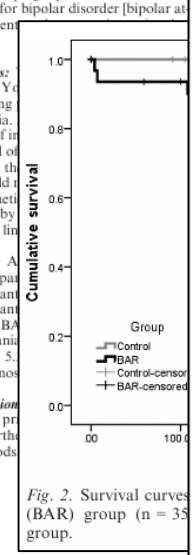


Fig. 2. Survival curves
(BAR) group (n = 35
group.

DOI: 10.1111/bdi.12831

REVIEW ARTICLE

BIPOLAR DISORDERS WILEY

An International Society of Bipolar Disorders task force report: Precursors and prodromes of bipolar disorder

Gianni L. Faedda[1,2] | Ross J. Baldessarini[2,3] | Ciro Marangoni[4] | Andreas Bechdolf[5,6] | Michael Berk[7,8,9] | Boris Birmaher[10] | Philippe Conus[11] | Melissa P. DelBello[12] | Anne C. Duffy[13] | Manon H. J. Hillegers[14,15] | Andrea Pfennig[16] | Robert M. Post[17,18] | Martin Preisig[19] | Aswin Ratheesh[7,8,9] | Paola Salvatore[3,20] | Mauricio Tohen[21] | Gustavo H. Vázquez[2,22] | Eduard Vieta[23] | Lakshmi N. Yatham[24] | Eric A. Youngstrom[25] | Anna Van Meter[26,27] | Christoph U. Correll[26,27,28,29]

[1]Mood Disorders Center, New York, NY, USA
[2]International Consortium for Mood and Psychotic Disorders Research, McLean Hospital, Belmont, MA, USA
[3]Department of Psychiatry, Harvard Medical School, Mailman Research Center, McLean Hospital, Boston, MA, USA
[4]Department of Psychiatry—District 3, ULSS 9 Scaligera, Verona, Italy
[5]Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany
[6]Department of Psychiatry, Psychotherapy and Psychosomatics, Vivantes Hospital am Urban and Vivantes Hospital im Friedrichshain, Charite Universitätsmedizin, Berlin, Germany
[7]IMPACT Strategic Research Centre, University Hospital Geelong, Barwon Health, Deakin University, Geelong, VIC, Australia
[8]Orygen, The National Center of Excellence in Youth Mental Health, Parkville, VIC, Australia
[9]The Florey Institute for Neuroscience and Mental Health and the Department of Psychiatry, University of Melbourne, Melbourne, VIC, Australia
[10]Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[11]Treatment and Early Intervention in Psychosis Program (TIPP), Département de Psychiatrie CHUV, Université de Lausanne, Lausanne, Switzerland
[12]Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH, USA
[13]Department of Psychiatry, Student Wellness Services, Queen's University, Kingston, ON, Canada
[14]Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands
[15]Department of Child and Adolescent Psychiatry, Erasmus medical Center Rotterdam, Rotterdam, The Netherlands
[16]Department of Psychiatry and Psychotherapy, Carl Gustav Carus University Hospital, Technische Universität Dresden, Dresden, Germany
[17]Bipolar Collaborative Network, Bethesda, MD, USA
[18]Department of Psychiatry, George Washington University School of Medicine, Washington, DC, USA
[19]Department of Psychiatry, University Hospital of Lausanne, Lausanne, Switzerland
[20]Psychiatry Section, Department of Neuroscience, School of Medicine, University of Parma, Parma, Italy
[21]Department of Psychiatry & Behavioral Sciences, University of New Mexico Health Sciences Center, Albuquerque, NM, USA
[22]Psychiatry, Queen's University, Kingston, ON, Canada
[23]Bipolar Disorder Unit, Institute of Neuroscience, Hospital Clinic, IDIBAPS, CIBERSAM, University of Barcelona, Barcelona, Spain
[24]Department of Psychiatry, Mood Disorders Centre, University of British Columbia, Vancouver, BD, Canada
[25]Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[26]Department of Psychiatry and Molecular Medicine, Hofstra Northwell School of Medicine, Hempstead, NY, USA
[27]The Zucker Hillside Hospital, Psychiatry Research, Northwell Health, Glen Oaks, NY, USA
[28]The Feinstein Institute for Medical Research, Center for Psychiatric Neuroscience, Manhasset, NY, USA
[29]Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany


Daymark Foundation
oxygen
Advancing
Early
Intervention
for
Bipolar
Disorder

The limitations in the prodromal phase and the ARMS concept

VOL. 22, NO. 2, 1996

The Prodromal Phase of First-Episode Psychosis: Past and Current Conceptualizations

by Alison R. Yung and Patrick D. McGorry

Abstract

The initial prodrome in psychosis is potentially important for early intervention, identification of biological markers, and understanding the process of becoming psychotic. This article reviews the previous literature on prodrome, including descriptions of symptoms and signs, and patterns and durations of prodromes in both schizophrenic and affective psychoses. Early detailed descriptions, achieved through mainly anecdotal reports, are compared with current conceptualizations, such as the *DSM–III–R* checklist of mainly behavioral items, which seeks to enhance reliability of measurement but at the expense of adequately describing the full range of phenomena. Current confusion about the nature of prodromal features and concerns regarding the reliability of their measurement are highlighted. This article proposes an alternative model for conceptualizing prodromal changes (the hybrid/interactive model) and discusses the different ways to view this phase. The need for a more systematic evaluation of the prodromal phase in first-episode psychosis is emphasized.

Schizophrenia Bulletin, 22(2): 353–370, 1996.

Defining the Term "Prodrome"

The term "prodrome" is derived from the Greek word *prodromos* meaning the forerunner of an event (Fava and Kellner 1991). In clinical medicine, a prodrome refers to the early symptoms and signs of an illness that precede the characteristic manifestations of the acute, fully developed illness. For example, measles is described as having a prodrome of 3 to 4 days characterized by fever, coryzal symptoms, conjunctivitis, and cough. This is followed by the specific rash, making definitive diagnosis possible (Yung and Stanley 1989). Prodrome in psychotic disorders is similarly defined. For example, Keith and Matthews (1991) defined it as "a heterogeneous group of behaviors temporally related to the onset of psychosis" (p. 53). The definition used by Loebel et al. (1992) was the time interval from onset of unusual behavioral symptoms to onset of psychotic symptoms. And Beiser et al. (1993) defined it as the period from first noticeable symptoms to first prominent psychotic symptoms. Essentially, the term refers to a period of prepsychotic disturbance, representing a deviation from a person's previous experience and behavior. As in clinical medicine, prodrome is a retrospective concept, diagnosed only after the development of definitive symptoms and signs.

The term "prodrome" has been used by some authors to denote the prepsychotic period before a relapse in those patients with established psychotic illnesses (Herz and Melville 1980; Birchwood et al. 1989; Malla and Norman 1994). This "relapse prodrome" should be distinguished from the prepsychotic period preceding the first onset of a psychotic illness, the "initial pro-

Reprint requests should be sent to Dr. A.R. Yung, Early Psychosis Prevention and Intervention Centre, 35 Poplar Rd., Parkville, Victoria 3052, Australia.

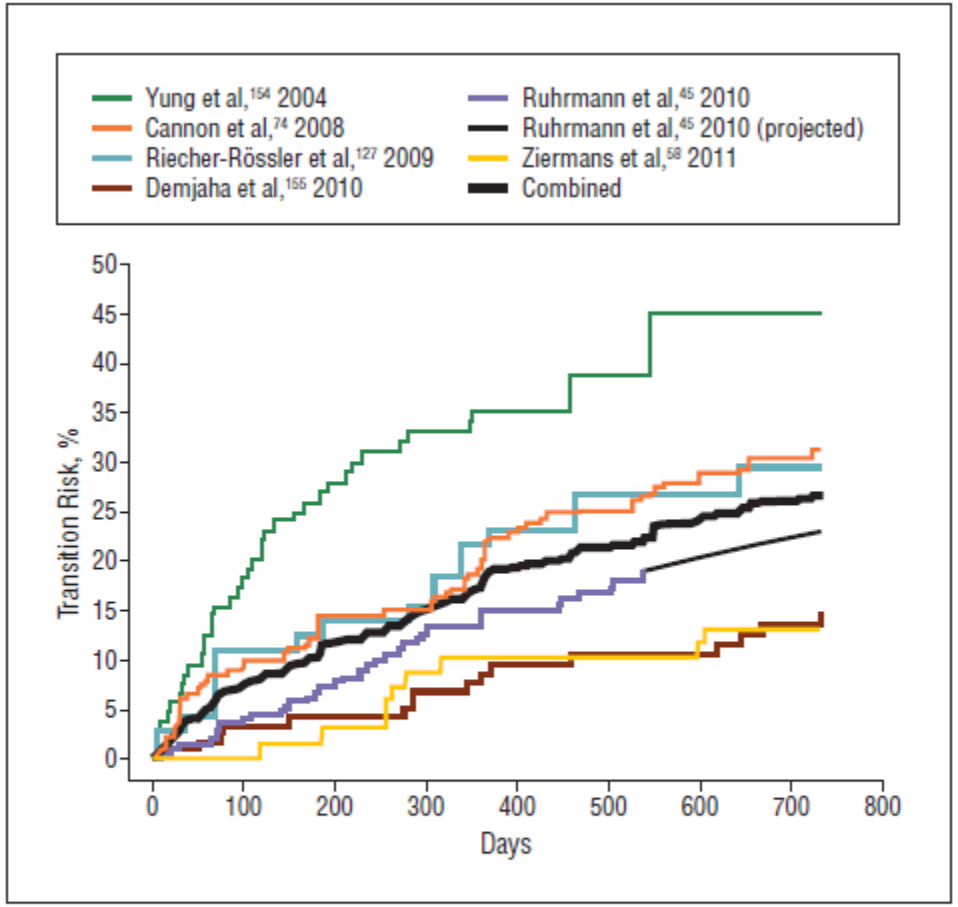
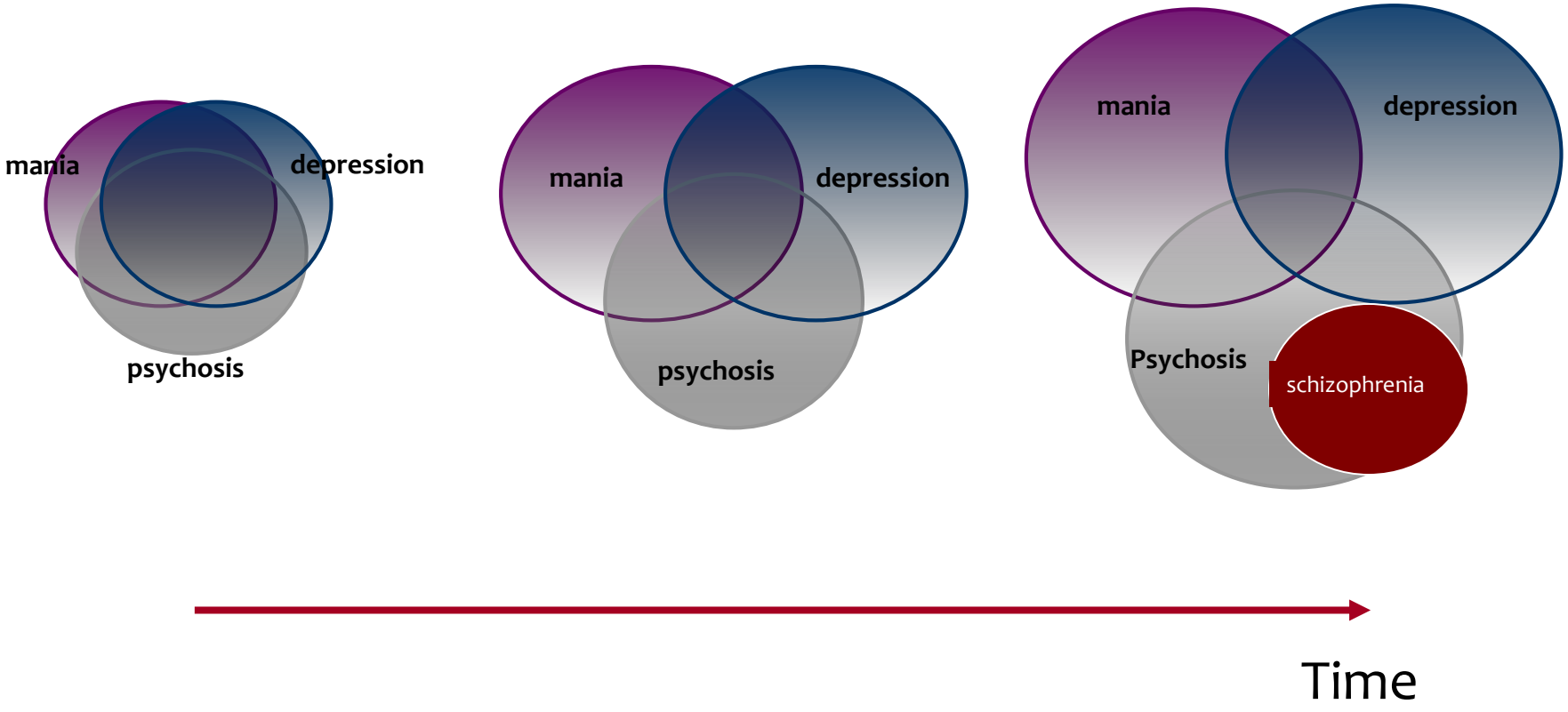
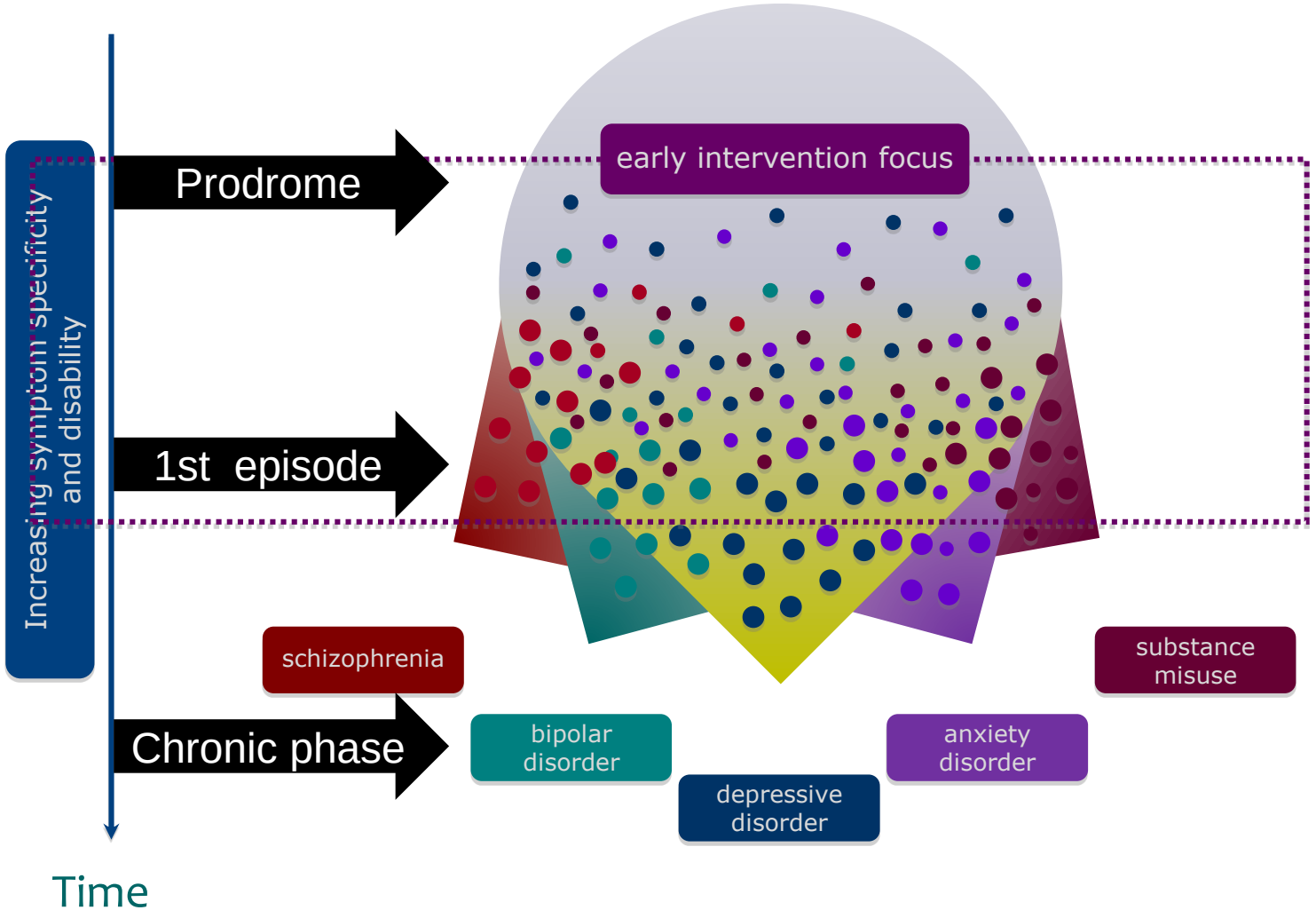


Figure 4. Meta-analysis of transition risks in studies reporting Kaplan-Meier estimates of psychosis transition over time in the high-risk state (n = 984 individuals) (for details of the study, see Fusar-Poli et al[75]). These risks are based on treated cohorts with no standardized treatment, so transition risk estimates are not for natural course or untreated cases.

Fusar Poli 2013

Pluripotential Early Stages with Growing Syndrome Clarity?

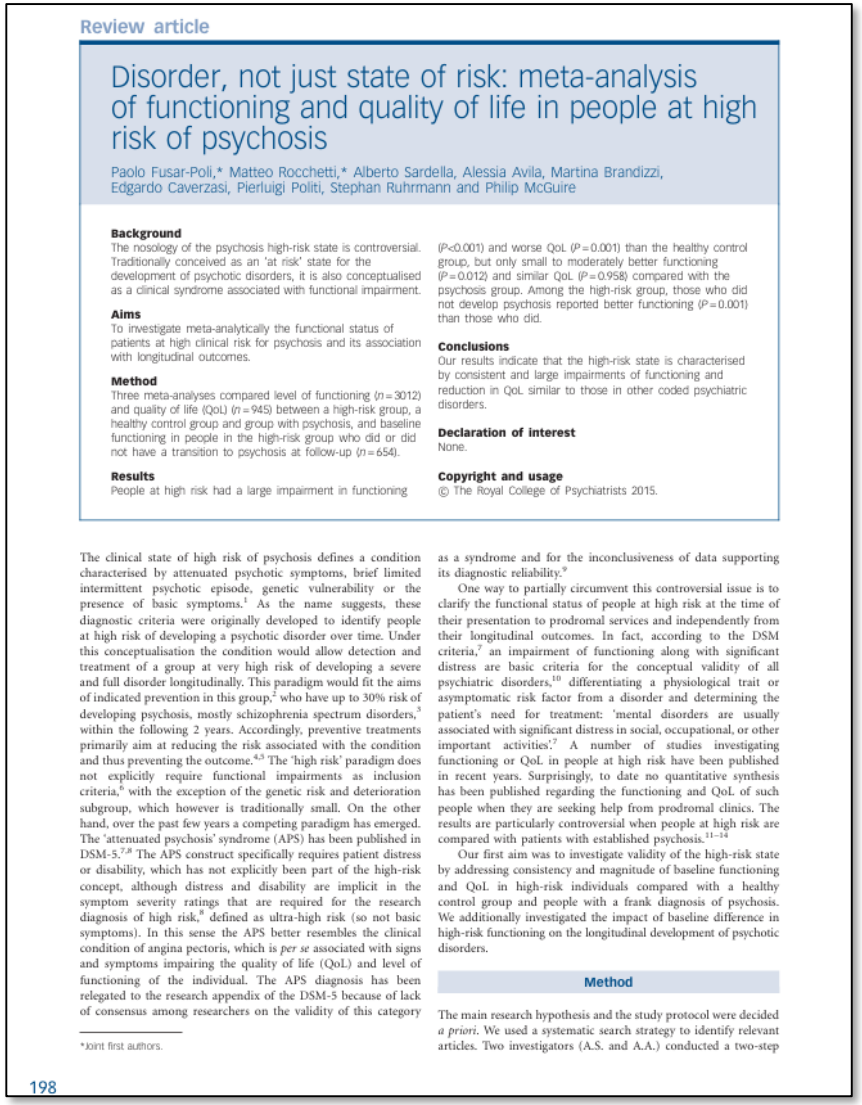



Increasing symptom specificity and disability
Prodrome
1st episode
Chronic phase
Time
early intervention focus
schizophrenia
bipolar disorder
depressive disorder
anxiety disorder
substance misuse

Problems with the ARMS concept

- Lack of specificity
- Low predictive value regarding transition to psychosis
- Lack of models for disorders other than psychosis
- LACK OF RELIABLE BIOMARKERS

- However, the ARMS syndrome is a disorder deserving treatment



Review article

Disorder, not just state of risk: meta-analysis of functioning and quality of life in people at high risk of psychosis

Paolo Fusar-Poli,* Matteo Rocchetti,* Alberto Sardella, Alessia Avila, Martina Brandizzi, Edgardo Caverzasi, Pierluigi Politi, Stephan Ruhrmann and Philip McGuire

Background
The nosology of the psychosis high-risk state is controversial. Traditionally conceived as an 'at risk' state for the development of psychotic disorders, it is also conceptualised as a clinical syndrome associated with functional impairment.

Aims
To investigate meta-analytically the functional status of patients at high clinical risk for psychosis and its association with longitudinal outcomes.

Method
Three meta-analyses compared level of functioning ($n=3012$) and quality of life (QoL) ($n=945$) between a high-risk group, a healthy control group and group with psychosis, and baseline functioning in people in the high-risk group who did or did not have a transition to psychosis at follow-up ($n=654$).

Results
People at high risk had a large impairment in functioning ($P<0.001$) and worse QoL ($P=0.001$) than the healthy control group, but only small to moderately better functioning ($P=0.012$) and similar QoL ($P=0.958$) compared with the psychosis group. Among the high-risk group, those who did not develop psychosis reported better functioning ($P=0.001$) than those who did.

Conclusions
Our results indicate that the high-risk state is characterised by consistent and large impairments of functioning and reduction in QoL similar to those in other coded psychiatric disorders.

Declaration of interest
None.

The clinical state of high risk of psychosis defines a condition characterised by attenuated psychotic symptoms, brief limited intermittent psychotic episode, genetic vulnerability or the presence of basic symptoms.[1] As the name suggests, these diagnostic criteria were originally developed to identify people at high risk of developing a psychotic disorder over time. Under this conceptualisation the condition would allow detection and treatment of a group at very high risk of developing a severe and full disorder longitudinally. This paradigm would fit the aims of indicated prevention in this group,[2] who have up to 30% risk of developing psychosis, mostly schizophrenia spectrum disorders,[3] within the following 2 years. Accordingly, preventive treatments primarily aim at reducing the risk associated with the condition and thus preventing the outcome.[4,5] The 'high risk' paradigm does not explicitly require functional impairments as inclusion criteria,[6] with the exception of the genetic risk and deterioration subgroup, which however is traditionally small. On the other hand, over the past few years a competing paradigm has emerged. The 'attenuated psychosis' syndrome (APS) has been published in DSM-5.[7,8] The APS construct specifically requires patient distress or disability, which has not explicitly been part of the high-risk concept, although distress and disability are implicit in the symptom severity ratings that are required for the research diagnosis of high risk,[8] defined as ultra-high risk (so not basic symptoms). In this sense the APS better resembles the clinical condition of angina pectoris, which is *per se* associated with signs and symptoms impairing the quality of life (QoL) and level of functioning of the individual. The APS diagnosis has been relegated to the research appendix of the DSM-5 because of lack of consensus among researchers on the validity of this category as a syndrome and for the inconclusiveness of data supporting its diagnostic reliability.[9]

One way to partially circumvent this controversial issue is to clarify the functional status of people at high risk at the time of their presentation to prodromal services and independently from their longitudinal outcomes. In fact, according to the DSM criteria,[7] an impairment of functioning along with significant distress are basic criteria for the conceptual validity of all psychiatric disorders,[10] differentiating a physiological trait or asymptomatic risk factor from a disorder and determining the patient's need for treatment: 'mental disorders are usually associated with significant distress in social, occupational, or other important activities'.[7] A number of studies investigating functioning or QoL in people at high risk have been published in recent years. Surprisingly, to date no quantitative synthesis has been published regarding the functioning and QoL of such people when they are seeking help from prodromal clinics. The results are particularly controversial when people at high risk are compared with patients with established psychosis.[11–14]

Our first aim was to investigate validity of the high-risk state by addressing consistency and magnitude of baseline functioning and QoL in high-risk individuals compared with a healthy control group and people with a frank diagnosis of psychosis. We additionally investigated the impact of baseline difference in high-risk functioning on the longitudinal development of psychotic disorders.

Method

The main research hypothesis and the study protocol were decided *a priori*. We used a systematic search strategy to identify relevant articles. Two investigators (A.S. and A.A.) conducted a two-step

*Joint first authors.

A similar problem with the staging concept

Stage	Description	Clinical features
0	Normal	No or few symptoms
0.5	Sub-threshold distress	Sub-threshold levels of anxiety and/or depression; corresponds approximately to sub-syndromal depression
1a	Distress disorder	Corresponds approximately to mild-to-moderate levels of DSM-IV MDE or GAD
1b	Distress disorder with ultra-high risk features	As for Stage 0.5 or above but with additional sub-threshold symptoms e.g.: •UHR psychotic symptoms •mood swings and irritability •phobic behaviour and/or ruminations that cause distress •substance misuse
2	First treated episode	Full-threshold DSM-IV diagnosable disorder
2a	First treated episode in remission	Remission from a first treated episode, after at least 6 months of evidence-based indicated treatment
2b	Recurrence	Relapse after recovery, after at least 6 months of remission from a first treated episode
3	Treatment resistance	No response to evidence-based indicated treatment for at least 6 months
4	Persistent disorder	

Very relevant concept for clinicians

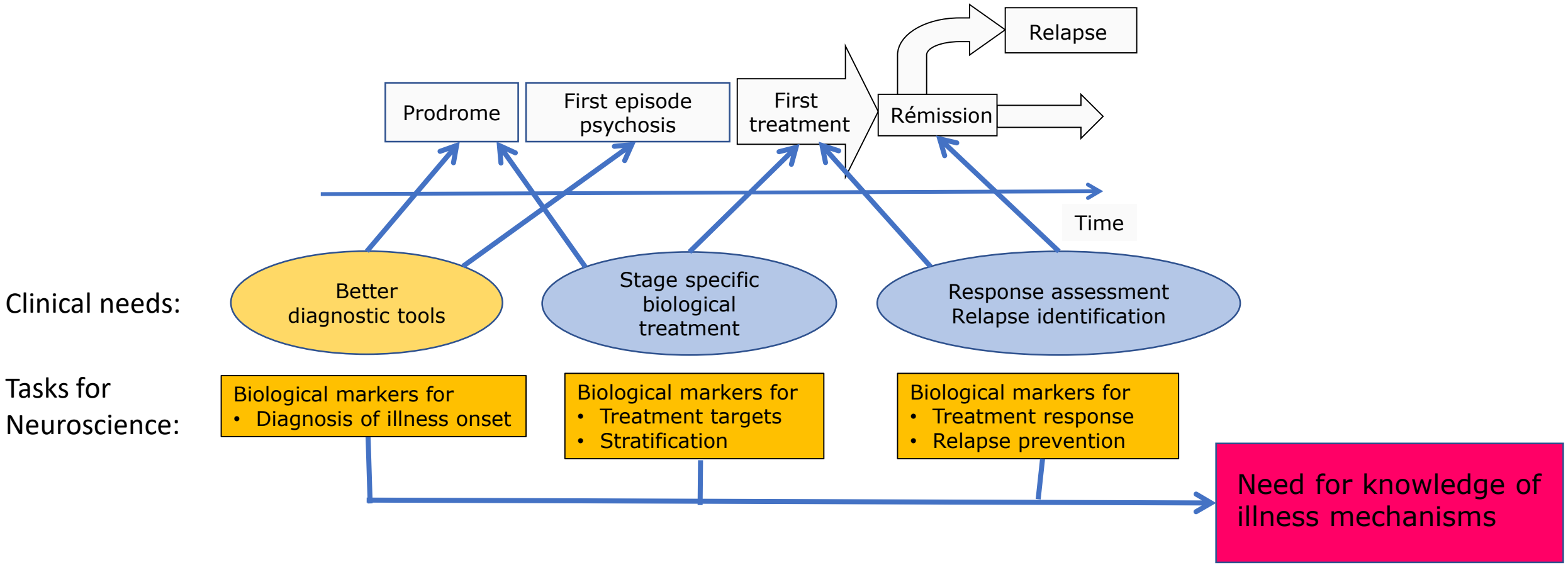
- Major challenges in defining stages
- Is the concept applicable to all disorders in the same way?

- Need for different biological treatments depending on stage

LACK OF RELIABLE BIOMARKERS

The neuro-biological challenge

Reaching the aims of early intervention: the role of neuro-biological research



synapsy
bringing together brain research and psychiatry
National Center of Competences in Research

UNIL | Université de Lausanne
CHUV

Research context in psychiatry in 2000

- **Clinicians in psychiatry:** Limited knowledge and interest in neurobiological determinants of disorders

- **Basic neuroscientists:** Focused on theoretical aspects and animal models and with limited links to psychiatric disorders

Credit: B. MELLOR

Translational research concept

PRECLINICAL MODEL

- ANIMAL MODELS
(Glutathion knock-out)
- DEVELOPMENT
(Genes – Environment)

GENETICS

MRS (brain)
METABOLOME (blood)
TRANSCRIPTOME (fibroblasts)

MORPHOLOGY (animals)
MRI
CONNECTIVITY (DSI)

NEUROPHYSIOLOGY
EEG

PSYCHOPATHOLOGY
NEUROPSYCHOLOGY
SOCIAL FUNCTIONING

CLINICAL COHORT

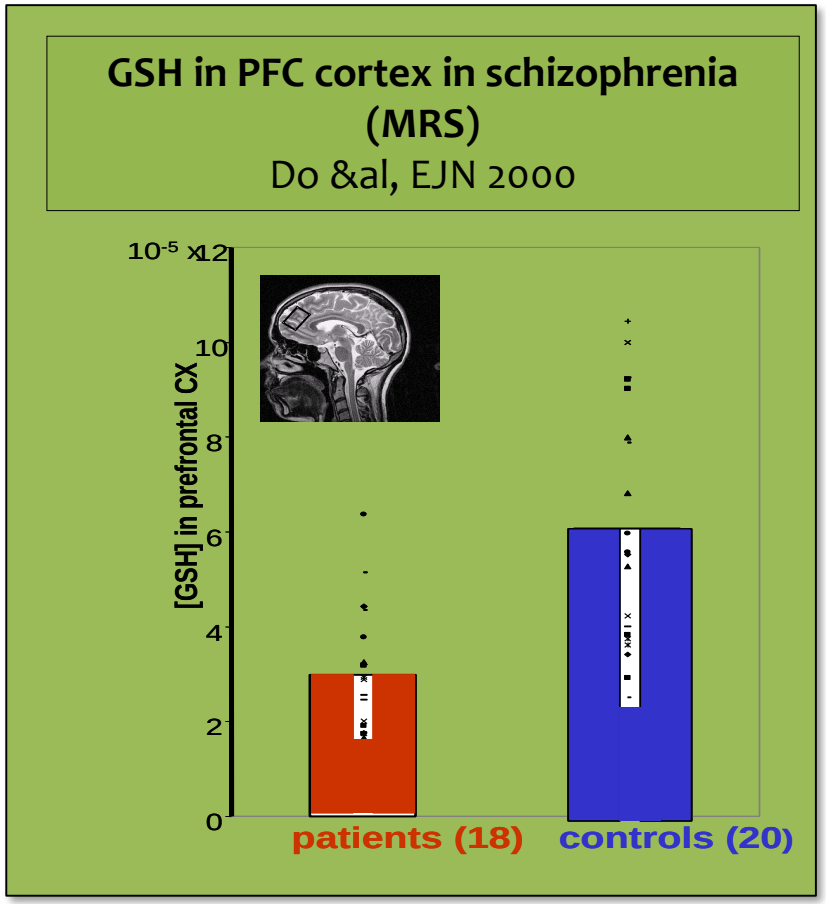
Clinical trials (various stages of illness) with new tratments/prevention

BIOMARKERS for
DIAGNOSIS & **MONITORING**

PATHOPHYSIOLOGY
THERAPEUTIC TARGETS

The NAC story: where it started

Prof. Kim Do



- **Context:**
  1. *Cerebral activity produces Reactive Oxygen Species (ROS) that are potentially deleterious to brain structure and function*
  2. *A good regulatory redox system is necessary*
  3. *Glutathion (GSH): the main cerebral antioxydant*

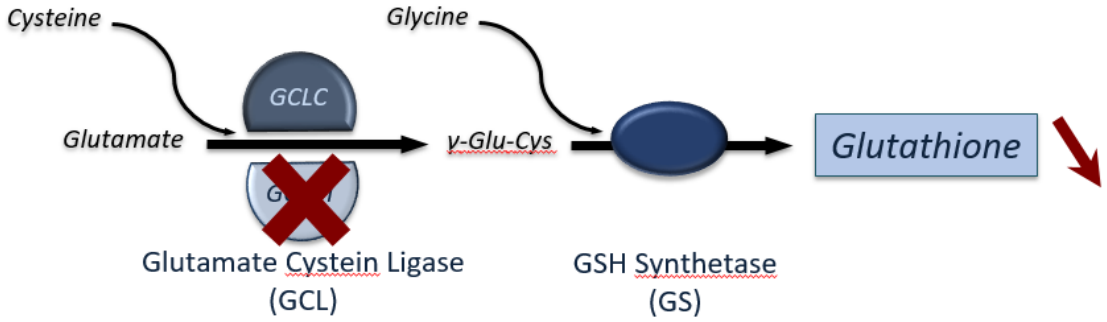
- **Initial observation: decreased GSH levels in the brain of schizophrenia patients** (CSF and brain spectroscopy)

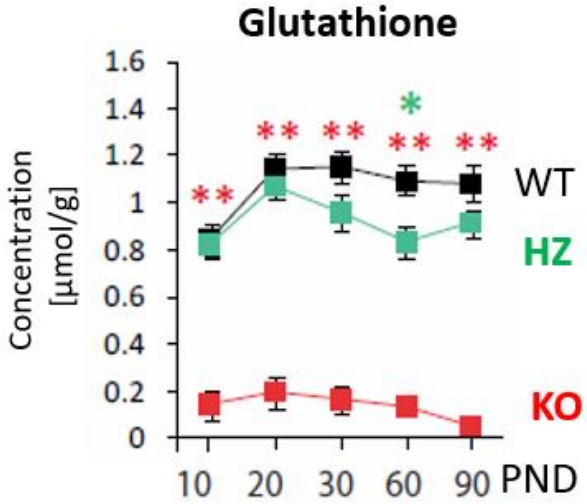
- **Hypothesis:** Redox imbalance, mainly regulated by GSH, may be a central mechanisms in schizophrenia

synapsy
bringing together brain research and psychiatry
National Center of Competences in Research

UNIL | Université de Lausanne
CHUV

The animal model: GCLM-KO mouse





Knockout mouse line lacking the gene encoding glutamate-cysteine ligase modifier (GCLM) subunit

GSH deficit (60-70% decrease) throughout brain structures and throughout life.

Yang &al., JBC 2002; Steullet, Cabungcal, & al. J Neurosci 2010

synapsy
bringing together brain research and psychiatry
National Center of Competences in Research

UNIL | Université de Lausanne
CHUV

TIPP: an early intervention program

- Inclusion criteria
  - Age 18 – 35
  - Less than 6 months antipsychotic treatment
  - Living in catchment area (330’000 inhabitants)
  - 3 years treatment
- Launched in 2004: > 1000 patients included
- Impact:
  - *Short delay to treatment: <2 months*
  - *High engagement rate: 5% drop out*
  - *Low rate of hospital admission: 0.8 admission per patient over 3 years*
- Longitudinal assessment

A lab of translational research

Translational approach
Clinical and preclinical models

Lausanne Psychosis Staging Research Program

ARMS | FEP | Long term psychosis

Assessment and clinical follow-up

Premorbid Baseline | **Psychopathol** | **Neuropsy** | **Functional level**

Multimodal biomarker profile

GENETICS | MRI / MRS | Metabolome transcriptome | EEG

synapsy
bringing together brain research and psychiatry
National Center of Competences in Research

UNIL | Université de Lausanne
CHUV

First step: to confirm a deficit of glutathione production in schizophrenia

PNAS | October 16, 2007 | vol. 104 | no. 42 | 16621–16626

Impaired glutathione synthesis in schizophrenia: Convergent genetic and functional evidence

René Gysin*†, Rudolf Kraftsik‡, Julie Sandell*, Pierre Bovet§, Céline Chappuis*, Philippe Conus§, Patricia Deppen*, Martin Preisig§, Viviane Ruiz*, Pascal Steullet*, Mirjana Tosic*, Thomas Werge¶, Michel Cuénod*, and Kim Q. Do*

*Center for Psychiatric Neuroscience and §Service of General Psychiatry, Department of Psychiatry, University Hospital Center and University of Lausanne, 1008 Prilly-Lausanne, Switzerland; †Department of Cellular Biology and Morphology, University of Lausanne, 1005 Lausanne, Switzerland; and ¶Research Institute of Biological Psychiatry, Copenhagen University Hospital, Sanct Hans Hospital, 4000 Roskilde, Denmark

Edited by Solomon H. Snyder, Johns Hopkins University School of Medicine, Baltimore, MD, and approved August 28, 2007 (received for review July 19, 2007)

Schizophrenia is a complex multifactorial brain disorder with a genetic component. Convergent evidence has implicated oxidative stress and glutathione (GSH) deficits in the pathogenesis of this disease. The aim of the present study was to test whether schizophrenia is associated with a deficit of GSH synthesis. Cultured skin fibroblasts from schizophrenia patients and control subjects were challenged with oxidative stress, and parameters of the rate-limiting enzyme for the GSH synthesis, the glutamate cysteine ligase (GCL), were measured. Stressed cells of patients had a 26% ($P = 0.002$) decreased GCL activity as compared with controls. This reduction correlated with a 29% ($P < 0.001$) decreased protein expression of the catalytic GCL subunit (GCLC). Genetic analysis of a trinucleotide repeat (TNR) polymorphism in the GCLC gene showed a significant association with schizophrenia in two independent case-control studies. The most common TNR genotype 7/7 was more frequent in controls [odds ratio (OR) = 0.6, $P = 0.003$], whereas the rarest TNR genotype 8/8 was three times more frequent in patients (OR = 3.0, $P = 0.007$). Moreover, subjects with disease-associated genotypes had lower GCLC protein expression ($P = 0.017$), GCL activity ($P = 0.037$), and GSH contents ($P = 0.004$) than subjects with genotypes that were more frequent in controls. Taken together, the study provides genetic and functional evidence that an impaired capacity to synthesize GSH under conditions of oxidative stress is a vulnerability factor for schizophrenia.

genetic association | glutamate cysteine ligase | oxidative stress | GAG trinucleotide repeat polymorphism | skin fibroblasts

Schizophrenia is a multifactorial disease with a strong heritable component. Although schizophrenia has begun to be studied on the level of molecular genetics, knowledge about genetically based functional alterations is sparse (1–4). Recent gene-expression analysis, genetic studies, and quantifications of brain glutathione (GSH) levels *in vivo* and on postmortem tissues led to the hypothesis that a dysregulation of the GSH metabolism is involved in the pathogenesis of schizophrenia (5–9). GSH levels were reduced by 27% in cerebrospinal fluid and by 52% in medial prefrontal cortex of schizophrenia patients (6). Similarly, GSH levels were decreased by 40% in the caudate region of postmortem-brain tissue from schizophrenia patients, as compared with control subjects (7).

GSH plays a crucial role as a cellular antioxidant scavenger of reactive oxygen species (ROS), and it maintains intracellular redox potential, detoxifies xenobiotics, and protects cells from oxidative thus particularly sensitive to an impaired capacity to react against oxidative stress (14).

Genetic polymorphisms or mutations that cause a deficit in GSH synthesis have been associated to various pathological processes or disorders, including oxidative stress (15), myocardial infarction (16), hemolytic anemia (17), neurological alterations, or mental retardation (18). Interestingly, an increased risk for cardiovascular morbidity has been described for schizophrenia (19, 20).

Cellular GSH levels are highly regulated (21), and several substances known to produce oxidative stress have been shown to increase GSH synthesis (22). GSH is synthesized in two consecutive enzymatic reactions: the first is catalyzed by the enzyme glutamate cysteine ligase (GCL) and the second by the GSH synthetase (GSS). GCL consists of a catalytic (GCLC) and a modulatory subunit (GCLM) (23). We recently reported a decrease in GCLM and GSS gene expression in cultured skin fibroblasts derived from schizophrenia patients, as compared with controls (8). The same study revealed a genetic association between allelic variants of the GCLM gene and schizophrenia.

The aim of the present study was to test whether schizophrenia is associated with a deficit in GSH synthesis. As a model, we selected fibroblasts that were obtained by skin biopsy. We supposed that a deficit in GSH synthesis is more pronounced under conditions of oxidative stress, and we thus treated cultured fibroblasts with *tert*-butylhydroquinone (t-BHQ), a substance known to increase the expression of phase II genes (including GCLM and GCLC), to increase GSH synthesis, and to increase GSH content (10, 24). We measured GSH content, GCL activity, as well as protein expression of GCLM and GCLC under baseline (untreated) and t-BHQ-treated conditions. We compared the regulation of GCLM and GCLC protein expression in relation to GCL activity and GSH content in patients and controls.

As GCLC protein expression and GCL activity were reduced in patients, the GCLC gene became our focus of interest. This gene was reported to contain a GAG trinucleotide repeat (TNR) polymorphism in the 5′-untranslated region (25). We compared the genotype distribution of this polymorphism in a Swiss sample of 66 schizophrenia patients and 48 control subjects and a Danish sample of 322 schizophrenia patients and 331 control subjects. Finally, we

Author contributions: R.G., M.C., and K.Q.D. designed research; R.G. and J.S. performed research; P.B., C.C., P.C., P.D., M.P., V.R., M.T., T.W., and K.Q.D. contributed new reagents/analytic tools; R.G., R.K., and P.S. analyzed data; and R.G. wrote the paper.

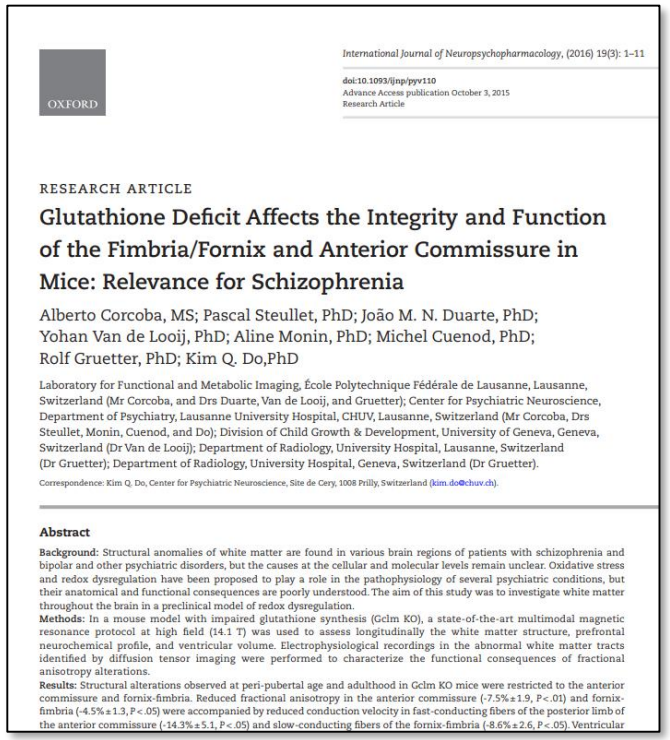
- **Methods:** Skin fibroblasts (of patients and controls) exposed to oxydative stress

- **Results and conclusion:**
  1. Schizophrenia patients as a group have a decreased capacity to synthesize GSH
  2. Some genetic profiles (high risk genotype) display a particular decrease
  3. Such genotypes are more frequent among patients than controls

synapsy
bringing together brain research and psychiatry
National Center of Competences in Research

UNIL | Université de Lausanne
CHUV

Impact of GSH deficit on white matter integrity



International Journal of Neuropsychopharmacology, (2016) 19(3): 1–11

doi:10.1093/ijnp/pyv110
Advance Access publication October 3, 2015
Research Article

RESEARCH ARTICLE

Glutathione Deficit Affects the Integrity and Function of the Fimbria/Fornix and Anterior Commissure in Mice: Relevance for Schizophrenia

Alberto Corcoba, MS; Pascal Steullet, PhD; João M. N. Duarte, PhD; Yohan Van de Looij, PhD; Aline Monin, PhD; Michel Cuenod, PhD; Rolf Gruetter, PhD; Kim Q. Do,PhD

Laboratory for Functional and Metabolic Imaging, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland (Mr Corcoba, and Drs Duarte, Van de Looij, and Gruetter); Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, CHUV, Lausanne, Switzerland (Mr Corcoba, Drs Steullet, Monin, Cuenod, and Do); Division of Child Growth & Development, University of Geneva, Geneva, Switzerland (Dr Van de Looij); Department of Radiology, University Hospital, Lausanne, Switzerland (Dr Gruetter); Department of Radiology, University Hospital, Geneva, Switzerland (Dr Gruetter).

Correspondence: Kim Q. Do, Center for Psychiatric Neuroscience, Site de Cery, 1008 Prilly, Switzerland (kim.do@chuv.ch).

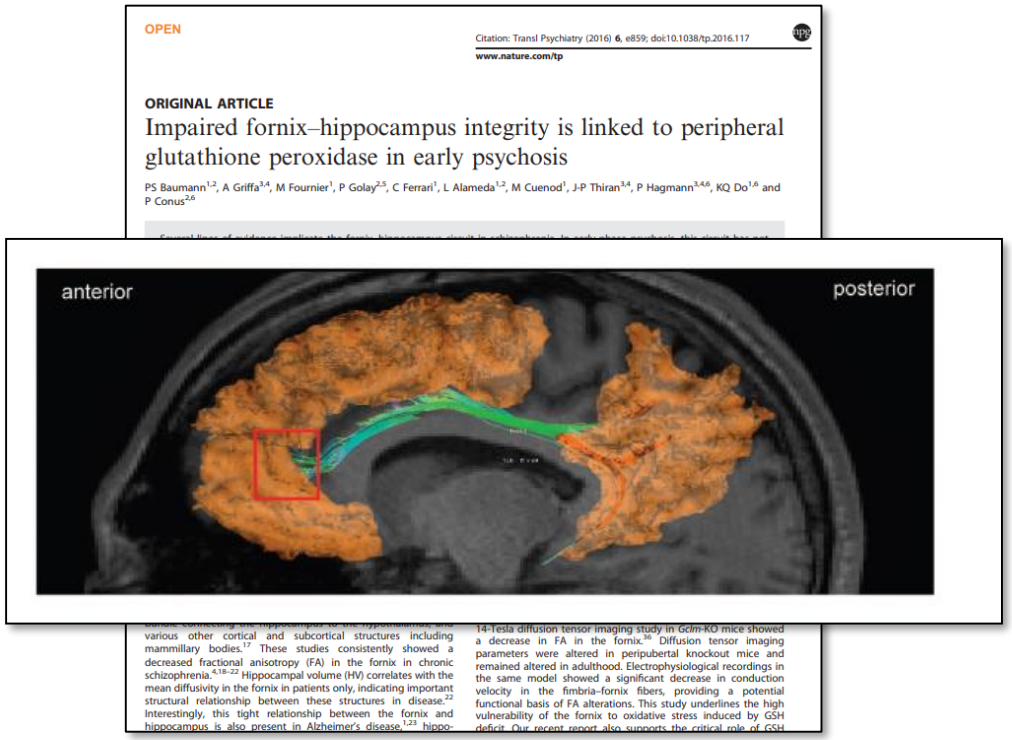
Abstract

Background: Structural anomalies of white matter are found in various brain regions of patients with schizophrenia and bipolar and other psychiatric disorders, but the causes at the cellular and molecular levels remain unclear. Oxidative stress and redox dysregulation have been proposed to play a role in the pathophysiology of several psychiatric conditions, but their anatomical and functional consequences are poorly understood. The aim of this study was to investigate white matter throughout the brain in a preclinical model of redox dysregulation.

Methods: In a mouse model with impaired glutathione synthesis (Gclm KO), a state-of-the-art multimodal magnetic resonance protocol at high field (14.1 T) was used to assess longitudinally the white matter structure, prefrontal neurochemical profile, and ventricular volume. Electrophysiological recordings in the abnormal white matter tracts identified by diffusion tensor imaging were performed to characterize the functional consequences of fractional anisotropy alterations.

Results: Structural alterations observed at peri-pubertal age and adulthood in Gclm KO mice were restricted to the anterior commissure and fornix-fimbria. Reduced fractional anisotropy in the anterior commissure (-7.5% ± 1.9, $P < .01$) and fornix-fimbria (-4.5% ± 1.3, $P < .05$) were accompanied by reduced conduction velocity in fast-conducting fibers of the posterior limb of the anterior commissure (-14.3% ± 5.1, $P < .05$) and slow-conducting fibers of the fornix-fimbria (-8.6% ± 2.6, $P < .05$). Ventricular

Glutathione deficit in Gclm KO mice affects the integrity of the fornix-fimbria and anterior commissure.



OPEN

Citation: Transl Psychiatry (2016) 6, e859; doi:10.1038/tp.2016.117
www.nature.com/tp

ORIGINAL ARTICLE

Impaired fornix–hippocampus integrity is linked to peripheral glutathione peroxidase in early psychosis

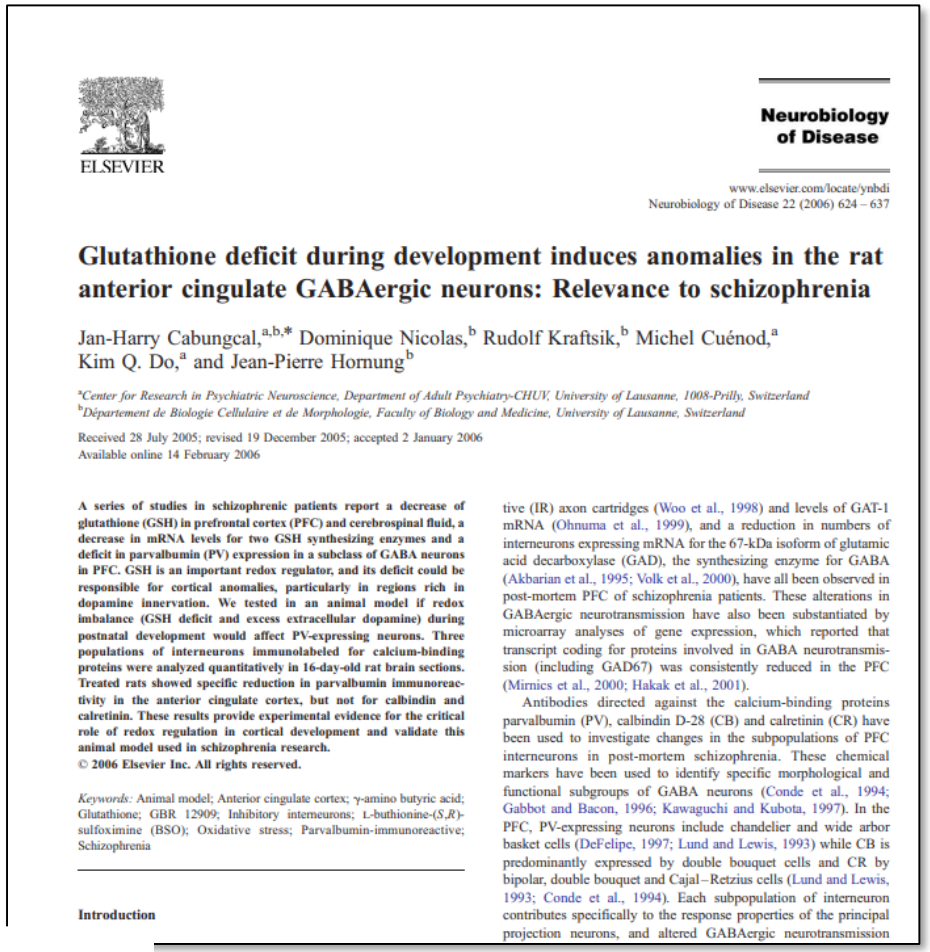
PS Baumann[1,2], A Griffa[3,4], M Fournier[1], P Golay[2,5], C Ferrari[1], L Alameda[1,2], M Cuenod[3], J-P Thiran[3,4], P Hagmann[3,4,6], KQ Do[1,6] and P Conus[2,6]

Impairment of white fibers integrity in the fornix of FEP patients compared to controls, correlation with GPX activity

synapsy
bringing together brain research and psychiatry
National Center of Competences in Research

UNIL | Université de Lausanne
CHUV

Impact of GSH deficit during development on PV cells



ELSEVIER

Neurobiology of Disease

www.elsevier.com/locate/ynbdi
Neurobiology of Disease 22 (2006) 624 – 637

Glutathione deficit during development induces anomalies in the rat anterior cingulate GABAergic neurons: Relevance to schizophrenia

Jan-Harry Cabungcal,[a,b,*] Dominique Nicolas,[b] Rudolf Kraftsik,[b] Michel Cuénod,[a] Kim Q. Do,[a] and Jean-Pierre Hornung[b]

[a]Center for Research in Psychiatric Neuroscience, Department of Adult Psychiatry-CHUV, University of Lausanne, 1008-Prilly, Switzerland
[b]Département de Biologie Cellulaire et de Morphologie, Faculty of Biology and Medicine, University of Lausanne, Switzerland

Received 28 July 2005; revised 19 December 2005; accepted 2 January 2006
Available online 14 February 2006

A series of studies in schizophrenic patients report a decrease of glutathione (GSH) in prefrontal cortex (PFC) and cerebrospinal fluid, a decrease in mRNA levels for two GSH synthesizing enzymes and a deficit in parvalbumin (PV) expression in a subclass of GABA neurons in PFC. GSH is an important redox regulator, and its deficit could be responsible for cortical anomalies, particularly in regions rich in dopamine innervation. We tested in an animal model if redox imbalance (GSH deficit and excess extracellular dopamine) during postnatal development would affect PV-expressing neurons. Three populations of interneurons immunolabeled for calcium-binding proteins were analyzed quantitatively in 16-day-old rat brain sections. Treated rats showed specific reduction in parvalbumin immunoreactivity in the anterior cingulate cortex, but not for calbindin and calretinin. These results provide experimental evidence for the critical role of redox regulation in cortical development and validate this animal model used in schizophrenia research.

Keywords: Animal model; Anterior cingulate cortex; γ-amino butyric acid; Glutathione; GBR 12909; Inhibitory interneurons; L-buthionine-(*S*,*R*)-sulfoximine (BSO); Oxidative stress; Parvalbumin-immunoreactive; Schizophrenia

Introduction

tive (IR) axon cartridges (Woo et al., 1998) and levels of GAT-1 mRNA (Ohnuma et al., 1999), and a reduction in numbers of interneurons expressing mRNA for the 67-kDa isoform of glutamic acid decarboxylase (GAD), the synthesizing enzyme for GABA (Akbarian et al., 1995; Volk et al., 2000), have all been observed in post-mortem PFC of schizophrenia patients. These alterations in GABAergic neurotransmission have also been substantiated by microarray analyses of gene expression, which reported that transcript coding for proteins involved in GABA neurotransmission (including GAD67) was consistently reduced in the PFC (Mirnics et al., 2000; Hakak et al., 2001).

Antibodies directed against the calcium-binding proteins parvalbumin (PV), calbindin D-28 (CB) and calretinin (CR) have been used to investigate changes in the subpopulations of PFC interneurons in post-mortem schizophrenia. These chemical markers have been used to identify specific morphological and functional subgroups of GABA neurons (Conde et al., 1994; Gabbot and Bacon, 1996; Kawaguchi and Kubota, 1997). In the PFC, PV-expressing neurons include chandelier and wide arbor basket cells (DeFelipe, 1997; Lund and Lewis, 1993) while CB is predominantly expressed by double bouquet cells and CR by bipolar, double bouquet and Cajal–Retzius cells (Lund and Lewis, 1993; Conde et al., 1994). Each subpopulation of interneuron contributes specifically to the response properties of the principal projection neurons, and altered GABAergic neurotransmission

- **Methods:**
  - Rats with GSH deficit exposed to excess extracellular dopamine during development
  - Exploration of impact on brain structure
- **Results:**
  - Treated rats showed **specific reduction in parvalbumin immunoreactivity in the anterior cingulate cortex**
- **Discussion:**
  - Redox regulation plays a central role in cortical development

synapsy
bringing together brain research and psychiatry
National Center of Competences in Research

UNIL | Université de Lausanne
CHUV

GSH deficit : one element of the more central mechanism of redox dysregulation

Contents lists available at ScienceDirect

Schizophrenia Research

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

Review

Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: A "central hub" in schizophrenia pathophysiology?

P. Steullet [a], J.H. Cabungcal [a], A. Monin [a], D. Dwir [a], P. O'Donnell [b], M. Cuenod [a], K.Q. Do [a]

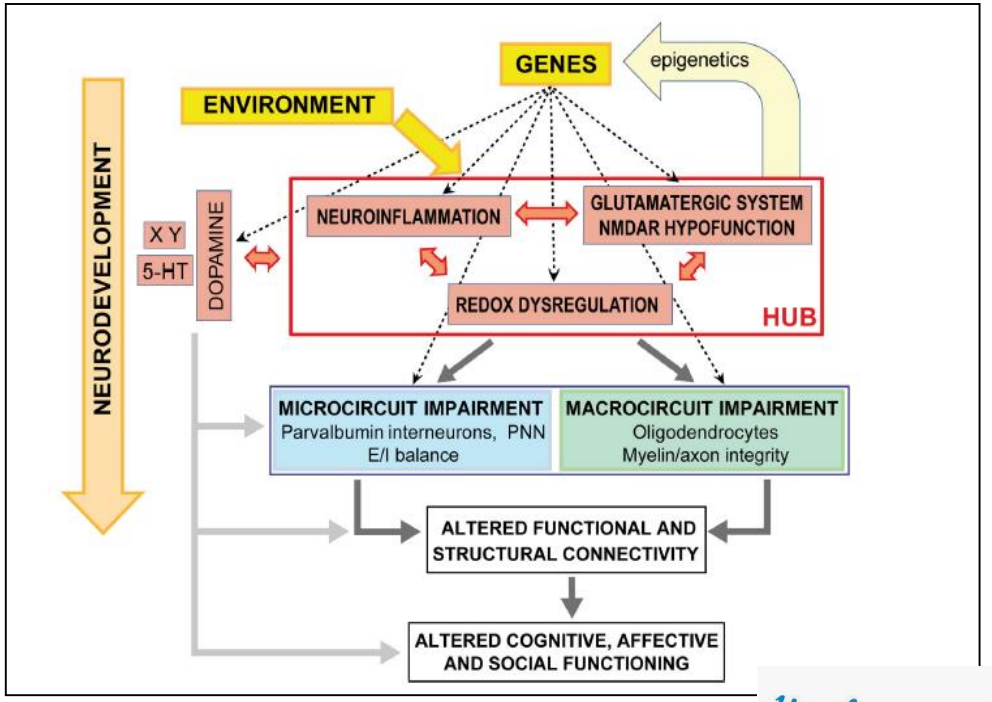
Schizophr Res. 2014

1. Various genetic and environmental risk factors for psychosis have been identified

2. Most of these risk factors induce, either directly or indirectly, redox dysregulation

3. The presence of redox dysregulation and oxydative stress during development induces

- Lesions of myeline and brain fiber tracts (alteration of structural connectivity)
- Lesions of PV celles (alteration of functional connectivity)

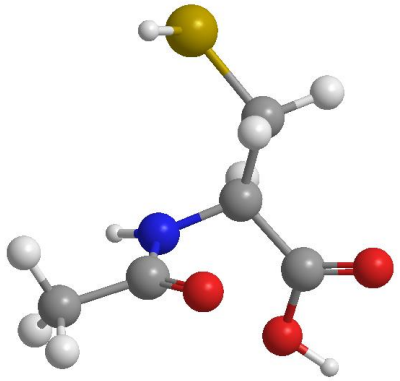


synapsy
bringing together brain research and psychiatry
National Center of Competences in Research

UNIL | Université de Lausanne

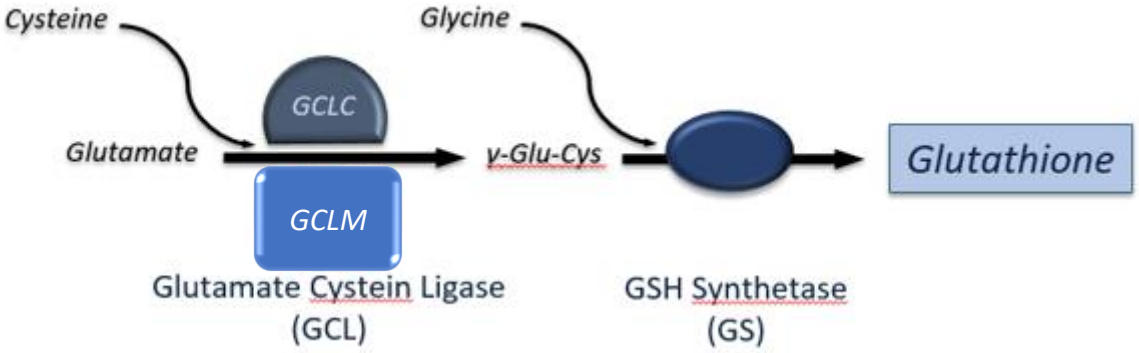
CHUV

Redox dysregulation: could NAC (N-Acétyl-Cytéine) be a solution?



- A simple molecule
- Sold over the counter
- Used in many other contexts
- Hardly any side effects

- **Contains the precursor of GSH (cystein)**
- **Hypothesis:** Oral administration of NAC may increase GSH levels in the brain and balance redox dysregulation
  - Restauration or protection of myeline?
  - Restauration or protection of PV-i?



synapsy
bringing together brain research and psychiatry
National Center of Competences in Research

UNIL | Université de Lausanne
CHUV

NAC in «chronic» schizophrenia patients

ARCHIVAL REPORTS BIOL PSYCHIATRY 2008;64:361–368

N-Acetyl Cysteine as a Glutathione Precursor for Schizophrenia—A Double-Blind, Randomized, Placebo-Controlled Trial

Michael Berk, David Copolov, Olivia Dean, Kristy Lu, Sue Jeavons, Ian Schapkaitz, Murray Anderson-Hunt, Fiona Judd, Fiona Katz, Paul Katz, Sean Ording-Jespersen, John Little, Philippe Conus, Michel Cuenod, Kim Q. Do, and Ashley I. Bush

Background: Brain glutathione levels are decreased in schizophrenia, a disorder that often is chronic and refractory to treatment. N-acetyl cysteine (NAC) increases brain glutathione in rodents. This study was conducted to evaluate the safety and effectiveness of oral NAC (1 g orally twice daily [b.i.d.]) as an add-on to maintenance medication for the treatment of chronic schizophrenia over a 24-week period.

Methods: A randomized, multicenter, double-blind, placebo-controlled study. The primary readout was change from baseline on the Positive and Negative Symptoms Scale (PANSS) and its components. Secondary readouts included the Clinical Global Impression (CGI) Severity and Improvement scales, as well as general functioning and extrapyramidal rating scales. Changes following a 4-week treatment discontinuation were evaluated. One hundred forty people with chronic schizophrenia on maintenance antipsychotic medication were randomized; 84 completed treatment.

Results: Intent-to-treat analysis revealed that subjects treated with NAC improved more than placebo-treated subjects over the study period in PANSS total [−5.97 (−10.44, −1.51), $p = .009$], PANSS negative [mean difference −1.83 (95% confidence interval: −3.33, −.32), $p = .018$], and PANSS general [−2.79 (−5.38, −.20), $p = .035$], CGI-Severity (CGI-S) [−.26 (−.44, −.08), $p = .004$], and CGI-Improvement (CGI-I) [−.22 (−.41, −.03), $p = .025$] scores. No significant change on the PANSS positive subscale was seen. N-acetyl cysteine treatment also was associated with an improvement in akathisia ($p = .022$). Effect sizes at end point were consistent with moderate benefits.

Conclusions: These data suggest that adjunctive NAC has potential as a safe and moderately effective augmentation strategy for chronic schizophrenia.

Key Words: Adjunct therapy, clinical trials, glutathione, n-acetyl cysteine, schizophrenia

Abnormalities of brain glutathione (GSH) metabolism in schizophrenia may offer a new target for pharmacological intervention. Glutathione, responsible for the detoxification of reactive oxygen and other radical species (1), is decreased (−27%) in the cerebrospinal fluid of drug-naïve patients with schizophrenia, reflecting a decrease in medial prefrontal cortex GSH (−52%) as detected by in vivo magnetic resonance spectroscopy (MRS) (2). Postmortem assay of the caudate region also showed a decrease of GSH (−41%) in patients with schizophrenia compared with normal control subjects (3). Polymorphisms in the genes for glutamate cysteine ligase modifier subunit (*gclm*) (4) and the catalytic subunit for glutamate cysteine ligase (*gclc*) (5), which both participate in GSH synthesis, suppress both protein expression and GSH levels and are linked to the risk for schizophrenia. Abnormal metabolism of neurotransmitters dopamine and glutamate, characteristic of schizophrenia, induce neuronal oxidative stress that is exaggerated by GSH deficiency (6–9).

We hypothesized that by augmenting production of GSH, N-acetyl cysteine (NAC) treatment may be of clinical benefit in the treatment of schizophrenia. Cysteine is the rate-limiting precursor for GSH synthesis, but oral supplementation with pure cysteine is not efficiently bioavailable (10,11). However, oral NAC rapidly increases plasma cysteine levels, replenishing depleted GSH pools systemically (12). Systemic administration of NAC prevents brain GSH depletion (13–18), with neuroprotective benefits in a variety of neurodegenerative disease models (19–23).

Our current aim was to study the efficacy and tolerability of 2 g daily (1 g twice daily [b.i.d.]) of NAC compared with placebo in patients with chronic schizophrenia who were being maintained on antipsychotics.

From The Mental Health Research Institute of Victoria (MB, DC, OD, AIB), Parkville; Department of Clinical and Biomedical Sciences (MB, KL, IS, MA-H), The University of Melbourne, Geelong; Orygen Youth Health (MB), Melbourne; Monash University (DC), Clayton; Department of Psychiatry (OD), The University of Melbourne, Parkville; Bendigo Health (SJ, FJ), Bendigo; Southwestern Health (FK, PK, SO-J), Melbourne; Ballarat Health (JL), Ballarat; and Department of Pathology (AIB), The University of Melbourne, Parkville, Australia; Department of Psychiatry (PC, MC, KQD), Lausanne University Hospital, Lausanne, Switzerland; and Department of Psychiatry (AIB), Massachusetts General Hospital, Charlestown, Massachusetts.

Address reprint requests to Ashley I. Bush, M.D., Ph.D., Department of Psy-

Methods and Materials

Study Design

The study was conducted from November 2002 until July 2005. Individuals were assigned using simple randomization (24) to treatment with NAC or placebo in a double-blind fashion. An independent coordinator generated the allocation sequence. The

- **CONTEXT AND AIM**:
  - N-Acetyl Cysteine is a precursor of glutathion
  - Aim: evaluating safety and effectiveness of oral NAC (2g/day) vs placebo as add on to usual treatment in patients with chronic schizophrenia
- **METHODS:**
  - RCT, double blind, multicenter, 24 weeks: 84 subjects: 2.7 grams/day
  - Outcome: PANNS, CGI, side effects
- **RESULTS**: Significanlty more improvement in NAC group on
  - **General and negative symptoms**
  - **Improvement of side effetcs (akathisia)**

synapsy
bringing together brain research and psychiatry
National Center of Competences in Research

UNIL | Université de Lausanne
CHUV

NAC in the early phase of psychosis

Schizophrenia Bulletin
doi:10.1093/schbul/sbx093

Schiz Bull 2018, 44(2):317-327

N-acetylcysteine in a Double-Blind Randomized Placebo-Controlled Trial: Toward Biomarker-Guided Treatment in Early Psychosis

Philippe Conus[1], Larry J. Seidman[2], Margot Fournier[3], Lijing Xin[4], Martine Cleusix[3], Philipp S. Baumann[1,3], Carina Ferrari[3], Ann Cousins[2], Luis Alameda[1,3], Mehdi Gholam-Rezaee[1], Philippe Golay[1], Raoul Jenni[3], T.-U. Wilson Woo[2,5], Matcheri S. Keshavan[2], Chin B. Eap[6,7] Joanne Wojcik[2], Michel Cuenod[3], Thierry Buclin[8], Rolf Gruetter[9], and Kim Q. Do*[,3]

[1]TIPP (Treatment and Early Intervention in Psychosis Program), Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital (CHUV), Lausanne, Switzerland; [2]Massachusetts Mental Health Center, Public Psychiatry Division of the Beth Israel, Deaconess Medical Center, Harvard Medical School, Department of Psychiatry, Boston, MA; [3]Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital (CHUV), Lausanne, Switzerland; [4]Animal Imaging and Technology Core (AIT), Center for Biomedical Imaging (CIBM), Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; [5]Department of Psychiatry, Harvard Medical School, McLean Hospital, Belmont, MA; [6]Department of Psychiatry, Unit of Pharmacogenetics and Clinical Psychopharmacology, Lausanne University Hospital (CHUV), Lausanne, Switzerland; [7]School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland; [8]Division of Clinical Pharmacology, Lausanne University Hospital (CHUV), Lausanne, Switzerland; [9]Laboratory of Functional and Metabolic Imaging, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

*To whom correspondence should be addressed; tel: +41-21-314-28-42, fax: +41-21-643-65-62, e-mail: kim.do@chuv.ch

Biomarker-guided treatments are needed in psychiatry, and previous data suggest oxidative stress may be a target in schizophrenia. A previous add-on trial with the antioxidant *N*-acetylcysteine (NAC) led to negative symptom reductions in chronic patients. We aim to study NAC's impact on symptoms and neurocognition in early psychosis (EP) and to explore whether glutathione (GSH)/redox markers could represent valid biomarkers to guide treatment. In a double-blind, randomized, placebo-controlled trial in 63 EP patients, we assessed the effect of NAC supplementation (2700 mg/day, 6 months) on PANSS, neurocognition, and redox markers (brain GSH [GSH_{mPFC}], blood cells GSH levels [GSH_{BC}], GSH peroxidase activity [GPx_{BC}]). No changes in negative or positive symptoms or functional outcome were observed with NAC, but significant improvements were found in favor of NAC on neurocognition (processing speed). NAC also led to increases of GSH_{mPFC} by 23% ($P = .005$) and GSH_{BC} by 19% ($P = .05$). In patients with high-baseline GPx_{BC} compared to low-baseline GPx_{BC}, subgroup explorations revealed a link between changes of positive symptoms and changes of redox status with NAC. GSH levels, could help identify a subgroup of patients who improve their positive symptoms with NAC. Thus, future trials with antioxidants in EP should consider biomarker-guided treatment.

Key words: glutathione/glutathione peroxidase/schizophrenia/MRS/prefrontal cortex/neurocognition

Introduction

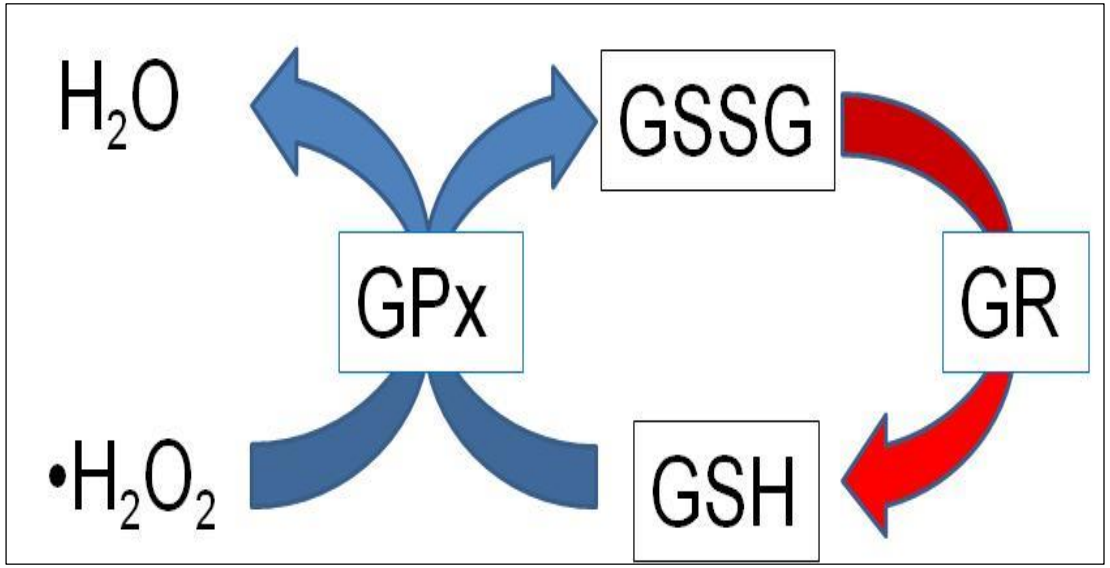
While early intervention improves the treatment of psychosis patients,[1] full benefits of these strategies are hampered by limited biological treatments. If antipsychotics improve positive symptoms, their efficacy on negative symptoms, neurocognition, social functioning, and quality of life is limited,[2–5] and their side effects impact treatment adherence negatively.[6] Poor knowledge regarding neurobiological mechanisms underlying psychotic disorders has limited pharmacological targets to altered D_2 neurotransmission[7] rather than more fundamental impairments. Despite improved understanding of the

- **AIMS:**
  - To explore impact of addition of NAC to standard treatment in early psychosis (EP) patients
- **HYPOTHESES:**
  - Role of redox dysregulation may be more important in the early phase of psychosis
  - Impact of NAC may be higher in this phase of the disorder
- **METHODS:**
  1. Double-blind, randomized, placebo-controlled trial of addition of NAC, 2700 mg daily, to antipsychotic treatment over 6 months.
  2. **Monthly assessment** of symptoms and functional level
  3. **Quantification of brain glutathione levels** (GSH_{mPFC}) by ^{1}H-magnetic-resonance-spectroscopy
  4. **Quantification of blood cells glutathione (GSH_{BC}) and glutathione peroxidase activity (GPx_{BC})** as marker of oxidation status at the beginning and end of treatment.

synapsy
bringing together brain research and psychiatry
National Center of Competences in Research

UNIL | Université de Lausanne
CHUV

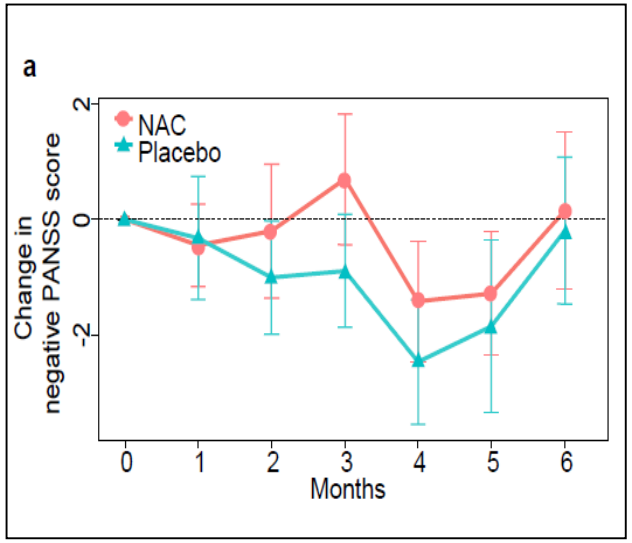
NAC in the early phase of psychosis



- High GPx levels correlates with high oxydative status
- GPx can be measured in the red blood cells

NAC in the early phase of psychosis

a



b

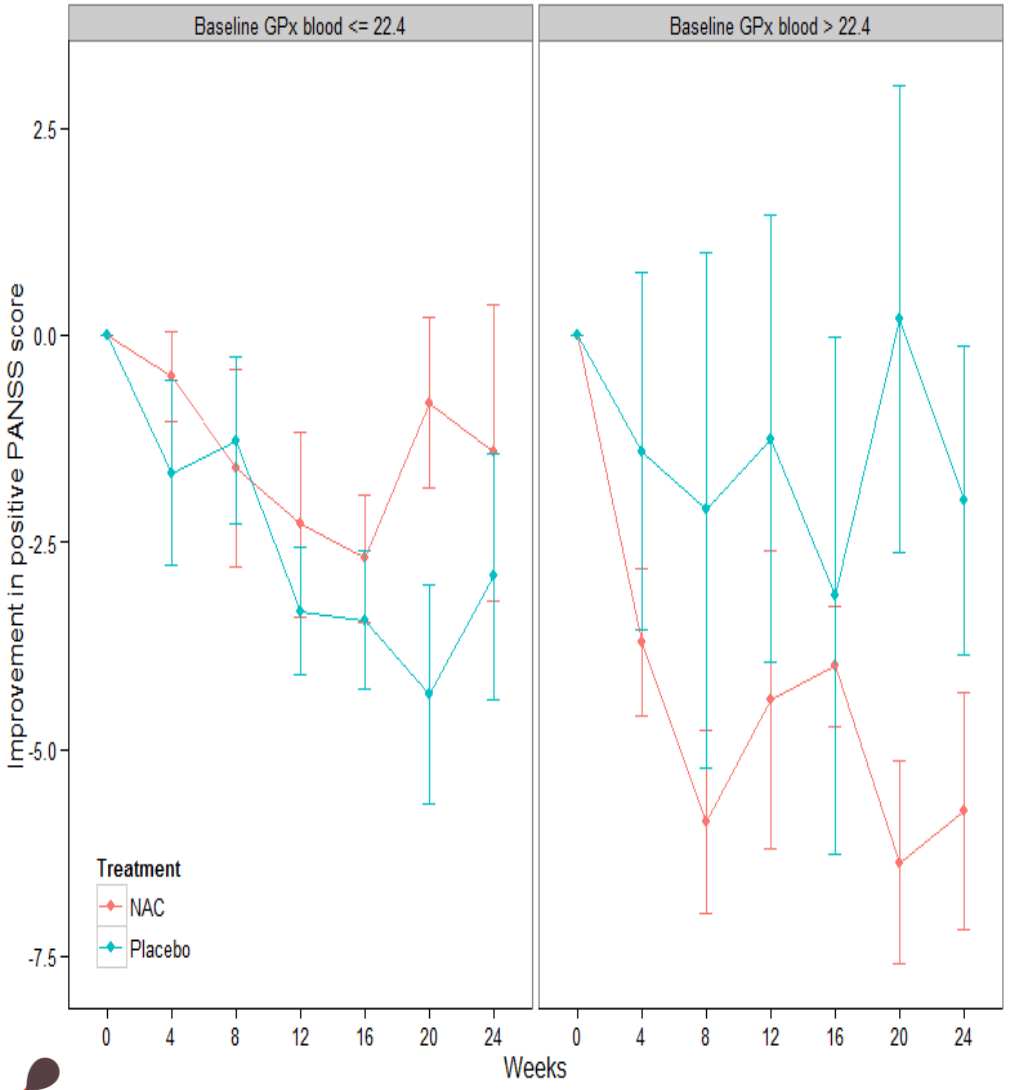
Clinical Domain	B	SE	P-value
PANSS negative	0.161	0.237	0.50
PANSS positive	0.176	0.207	0.39
PANSS general	0.598	0.359	0.09
GAF	-0.332	0.515	0.52
SOFAS	-0.196	0.527	0.71

1. 63 patients were included (32 NAC; 31 placebo).
2. **Spectroscopy:** NAC induces an increase in brain glutathion levels in the brain (p=0.005).
3. **Clinical assessment:**
    1. Improvement of processing speed
    2. No significant difference in negative symptoms, positive symptoms or functional outcome.

synapsy
bringing together brain research and psychiatry
National Center of Competence in Research

UNIL | Université de Lausanne
CHUV

NAC in the early phase of psychosis



Stratification based on peripheral oxydative status at baseline

Among patients high oxidative status at baseline (GPxBC >22.3U/gHb) patients with NAC, compared to placebo, displayed significantly greater :

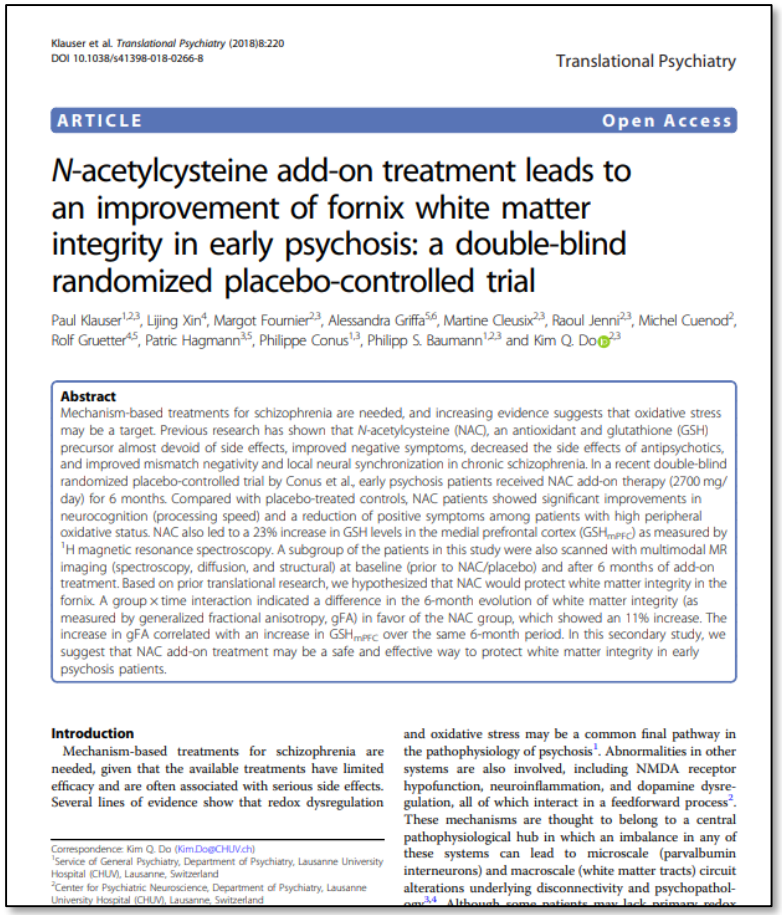
1. ***Improvement in positive symptoms*** *(p=0.02).*
2. ***improvement in cognitive function*** *(verbal memory, working memory, speed processing) (p= 0.023/ 0.048/ 0.022)*

3. ***The greater the decrease in peripheral GPx, the greater the clinical improvement***

synapsy
bringing together brain research and psychiatry
National Center of Competences in Research

UNIL | Université de Lausanne
CHUV

NAC in the early phase of psychosis: impact on white matter integrity



Klauser et al. *Translational Psychiatry* (2018)8:220
DOI 10.1038/s41398-018-0266-8

Translational Psychiatry

ARTICLE Open Access

N-acetylcysteine add-on treatment leads to an improvement of fornix white matter integrity in early psychosis: a double-blind randomized placebo-controlled trial

Paul Klauser[1,2,3], Lijing Xin[4], Margot Fournier[2,3], Alessandra Griffa[5,6], Martine Cleusix[2,3], Raoul Jenni[2,3], Michel Cuenod[2], Rolf Gruetter[4,5], Patric Hagmann[3,5], Philippe Conus[1,3], Philipp S. Baumann[1,2,3] and Kim Q. Do[2,3]

Abstract
Mechanism-based treatments for schizophrenia are needed, and increasing evidence suggests that oxidative stress may be a target. Previous research has shown that *N*-acetylcysteine (NAC), an antioxidant and glutathione (GSH) precursor almost devoid of side effects, improved negative symptoms, decreased the side effects of antipsychotics, and improved mismatch negativity and local neural synchronization in chronic schizophrenia. In a recent double-blind randomized placebo-controlled trial by Conus et al., early psychosis patients received NAC add-on therapy (2700 mg/day) for 6 months. Compared with placebo-treated controls, NAC patients showed significant improvements in neurocognition (processing speed) and a reduction of positive symptoms among patients with high peripheral oxidative status. NAC also led to a 23% increase in GSH levels in the medial prefrontal cortex (GSH_{mPFC}) as measured by ^{1}H magnetic resonance spectroscopy. A subgroup of the patients in this study were also scanned with multimodal MR imaging (spectroscopy, diffusion, and structural) at baseline (prior to NAC/placebo) and after 6 months of add-on treatment. Based on prior translational research, we hypothesized that NAC would protect white matter integrity in the fornix. A group × time interaction indicated a difference in the 6-month evolution of white matter integrity (as measured by generalized fractional anisotropy, gFA) in favor of the NAC group, which showed an 11% increase. The increase in gFA correlated with an increase in GSH_{mPFC} over the same 6-month period. In this secondary study, we suggest that NAC add-on treatment may be a safe and effective way to protect white matter integrity in early psychosis patients.

Introduction
Mechanism-based treatments for schizophrenia are needed, given that the available treatments have limited efficacy and are often associated with serious side effects. Several lines of evidence show that redox dysregulation and oxidative stress may be a common final pathway in the pathophysiology of psychosis[1]. Abnormalities in other systems are also involved, including NMDA receptor hypofunction, neuroinflammation, and dopamine dysregulation, all of which interact in a feedforward process[2]. These mechanisms are thought to belong to a central pathophysiological hub in which an imbalance in any of these systems can lead to microscale (parvalbumin interneurons) and macroscale (white matter tracts) circuit alterations underlying disconnectivity and psychopathology[3,4]. Although some patients may lack primary redox

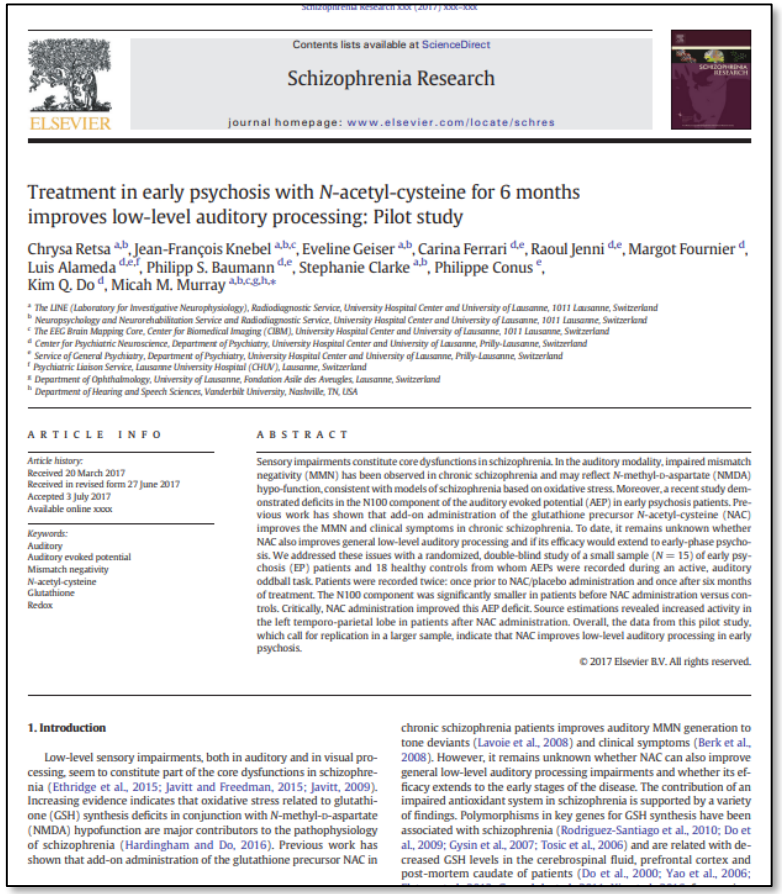
Correspondence: Kim Q. Do (Kim.Do@CHUV.ch)
[1]Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital (CHUV), Lausanne, Switzerland
[2]Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital (CHUV), Lausanne, Switzerland

N-acetyl-cysteine supplementation has a positive effect on **white matter integrity** in early psychosis patients

synapsy
bringing together brain research and psychiatry
National Center of Competences in Research

UNIL | Université de Lausanne
CHUV

NAC in the early phase of psychosis: impact on low-level auditory processing



Contents lists available at ScienceDirect

Schizophrenia Research

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

Treatment in early psychosis with *N*-acetyl-cysteine for 6 months improves low-level auditory processing: Pilot study

Chrysa Retsa [a,b], Jean-François Knebel [a,b,c], Eveline Geiser [a,b], Carina Ferrari [d,e], Raoul Jenni [d,e], Margot Fournier [d], Luis Alameda [d,e,f], Philipp S. Baumann [d,e], Stephanie Clarke [a,b], Philippe Conus [e], Kim Q. Do [d], Micah M. Murray [a,b,c,g,h,*]

[a] The LINE (Laboratory for Investigative Neurophysiology), Radiodiagnostic Service, University Hospital Center and University of Lausanne, 1011 Lausanne, Switzerland
[b] Neuropsychology and Neurorehabilitation Service and Radiodiagnostic Service, University Hospital Center and University of Lausanne, 1011 Lausanne, Switzerland
[c] The EEG Brain Mapping Core, Center for Biomedical Imaging (CIBM), University Hospital Center and University of Lausanne, 1011 Lausanne, Switzerland
[d] Center for Psychiatric Neuroscience, Department of Psychiatry, University Hospital Center and University of Lausanne, Prilly-Lausanne, Switzerland
[e] Service of General Psychiatry, Department of Psychiatry, University Hospital Center and University of Lausanne, Prilly-Lausanne, Switzerland
[f] Psychiatric Liaison Service, Lausanne University Hospital (CHUV), Lausanne, Switzerland
[g] Department of Ophthalmology, University of Lausanne, Fondation Asile des Aveugles, Lausanne, Switzerland
[h] Department of Hearing and Speech Sciences, Vanderbilt University, Nashville, TN, USA

ARTICLE INFO

Article history:
Received 20 March 2017
Received in revised form 27 June 2017
Accepted 3 July 2017
Available online xxxx

Keywords:
Auditory
Auditory evoked potential
Mismatch negativity
N-acetyl-cysteine
Glutathione
Redox

ABSTRACT

Sensory impairments constitute core dysfunctions in schizophrenia. In the auditory modality, impaired mismatch negativity (MMN) has been observed in chronic schizophrenia and may reflect *N*-methyl-D-aspartate (NMDA) hypo-function, consistent with models of schizophrenia based on oxidative stress. Moreover, a recent study demonstrated deficits in the N100 component of the auditory evoked potential (AEP) in early psychosis patients. Previous work has shown that add-on administration of the glutathione precursor *N*-acetyl-cysteine (NAC) improves the MMN and clinical symptoms in chronic schizophrenia. To date, it remains unknown whether NAC also improves general low-level auditory processing and if its efficacy would extend to early-phase psychosis. We addressed these issues with a randomized, double-blind study of a small sample ($N = 15$) of early psychosis (EP) patients and 18 healthy controls from whom AEPs were recorded during an active, auditory oddball task. Patients were recorded twice: once prior to NAC/placebo administration and once after six months of treatment. The N100 component was significantly smaller in patients before NAC administration versus controls. Critically, NAC administration improved this AEP deficit. Source estimations revealed increased activity in the left temporo-parietal lobe in patients after NAC administration. Overall, the data from this pilot study, which call for replication in a larger sample, indicate that NAC improves low-level auditory processing in early psychosis.

1. Introduction

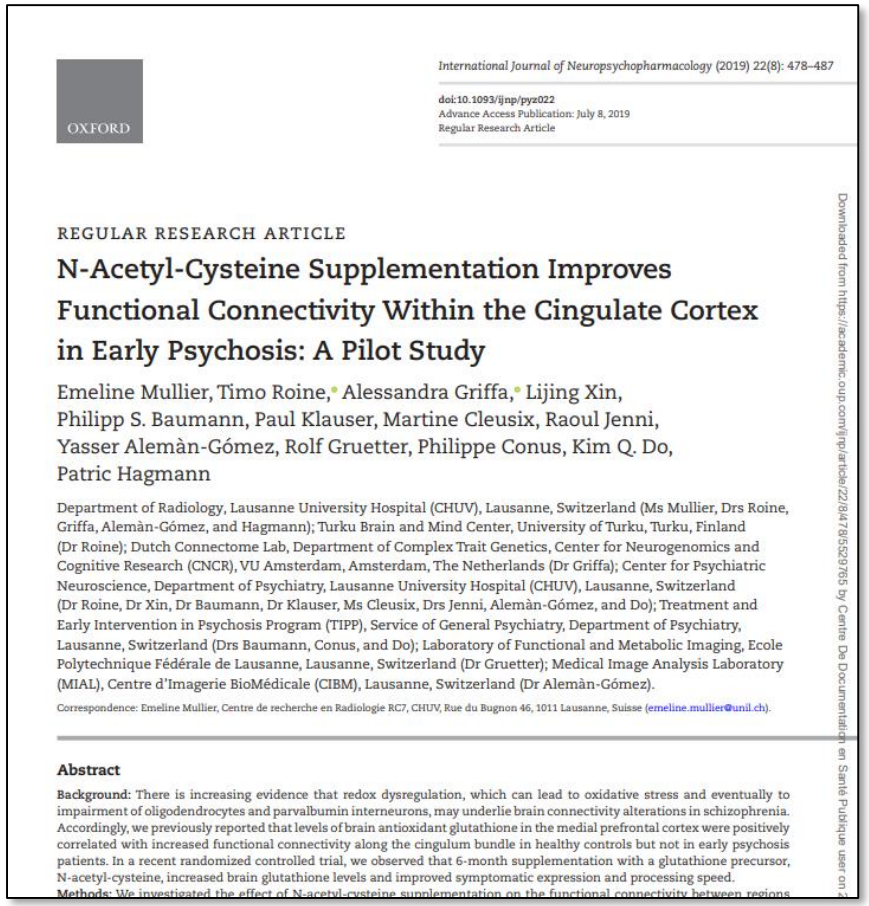
Low-level sensory impairments, both in auditory and in visual processing, seem to constitute part of the core dysfunctions in schizophrenia (Ethridge et al., 2015; Javitt and Freedman, 2015; Javitt, 2009). Increasing evidence indicates that oxidative stress related to glutathione (GSH) synthesis deficits in conjunction with *N*-methyl-D-aspartate (NMDA) hypofunction are major contributors to the pathophysiology of schizophrenia (Hardingham and Do, 2016). Previous work has shown that add-on administration of the glutathione precursor NAC in chronic schizophrenia patients improves auditory MMN generation to tone deviants (Lavoie et al., 2008) and clinical symptoms (Berk et al., 2008). However, it remains unknown whether NAC can also improve general low-level auditory processing impairments and whether its efficacy extends to the early stages of the disease. The contribution of an impaired antioxidant system in schizophrenia is supported by a variety of findings. Polymorphisms in key genes for GSH synthesis have been associated with schizophrenia (Rodriguez-Santiago et al., 2010; Do et al., 2009; Gysin et al., 2007; Tosic et al., 2006) and are related with decreased GSH levels in the cerebrospinal fluid, prefrontal cortex and post-mortem caudate of patients (Do et al., 2000; Yao et al., 2006;

N-acetyl-cysteine supplementation has a positive effect on **low level auditory processing** in early psychosis patients

synapsy
bringing together brain research and psychiatry
National Center of Competences in Research

UNIL | Université de Lausanne
CHUV

NAC in the early phase of psychosis: impact on functional connectivity within cingulate cortex



International Journal of Neuropsychopharmacology (2019) 22(8): 478–487

doi:10.1093/ijnp/pyz022
Advance Access Publication: July 8, 2019
Regular Research Article

REGULAR RESEARCH ARTICLE

N-Acetyl-Cysteine Supplementation Improves Functional Connectivity Within the Cingulate Cortex in Early Psychosis: A Pilot Study

Emeline Mullier, Timo Roine,* Alessandra Griffa,* Lijing Xin, Philipp S. Baumann, Paul Klauser, Martine Cleusix, Raoul Jenni, Yasser Alemàn-Gómez, Rolf Gruetter, Philippe Conus, Kim Q. Do, Patric Hagmann

Department of Radiology, Lausanne University Hospital (CHUV), Lausanne, Switzerland (Ms Mullier, Drs Roine, Griffa, Alemàn-Gómez, and Hagmann); Turku Brain and Mind Center, University of Turku, Turku, Finland (Dr Roine); Dutch Connectome Lab, Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research (CNCR), VU Amsterdam, Amsterdam, The Netherlands (Dr Griffa); Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital (CHUV), Lausanne, Switzerland (Dr Roine, Dr Xin, Dr Baumann, Dr Klauser, Ms Cleusix, Drs Jenni, Alemàn-Gómez, and Do); Treatment and Early Intervention in Psychosis Program (TIPP), Service of General Psychiatry, Department of Psychiatry, Lausanne, Switzerland (Drs Baumann, Conus, and Do); Laboratory of Functional and Metabolic Imaging, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland (Dr Gruetter); Medical Image Analysis Laboratory (MIAL), Centre d'Imagerie BioMédicale (CIBM), Lausanne, Switzerland (Dr Alemàn-Gómez).

Correspondence: Emeline Mullier, Centre de recherche en Radiologie RC7, CHUV, Rue du Bugnon 46, 1011 Lausanne, Suisse (emeline.mullier@unil.ch).

Abstract

Background: There is increasing evidence that redox dysregulation, which can lead to oxidative stress and eventually to impairment of oligodendrocytes and parvalbumin interneurons, may underlie brain connectivity alterations in schizophrenia. Accordingly, we previously reported that levels of brain antioxidant glutathione in the medial prefrontal cortex were positively correlated with increased functional connectivity along the cingulum bundle in healthy controls but not in early psychosis patients. In a recent randomized controlled trial, we observed that 6-month supplementation with a glutathione precursor, N-acetyl-cysteine, increased brain glutathione levels and improved symptomatic expression and processing speed.

Methods: We investigated the effect of N-acetyl-cysteine supplementation on the functional connectivity between regions

N-acetyl-cysteine supplementation has a positive effect on **functional connectivity within the cingulate cortex** in early psychosis patients

synapsy
bringing together brain research and psychiatry
National Center of Competences in Research

UNIL | Université de Lausanne

CHUV

Conclusion

- Redox dysregulation could be a central mechanism in psychosis
- NAC in early psychosis patients has a positive impact on
  - *Cognition (processing speed), White matter intergrity, Low level auditory processing, Functional connectivity*
- In early psychosis patients with high level of oxydative stress, NAC has a positive impact on positive symptoms and cognition
- A FIRST STEP TOWARDS BIOMARKER GUIDED TREATMENT

- We need more of such research on mechanisms in order to
  - Identify treatment targets
  - Delineate stages of illness
  - Idenfiy biomarkers of disorder and /or stages

The political challenge

REVIEW ARTICLE

OPEN

Early Intervention in Psychosis

Obvious, Effective, Overdue

Patrick D. McGorry, MD, PhD, FRCP, FRANZCP

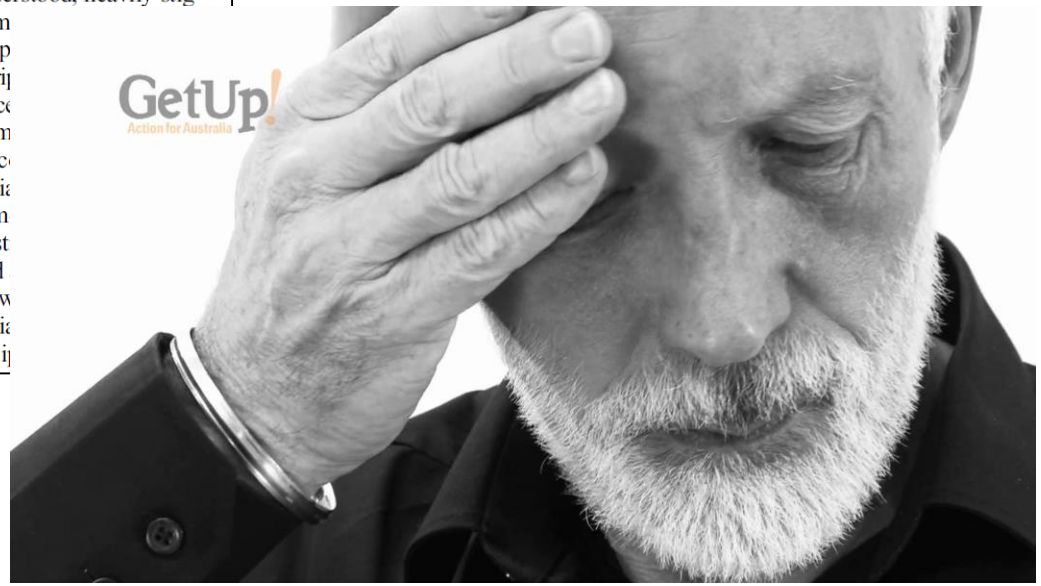
Abstract: Early intervention for potentially serious disorder is a fundamental feature of healthcare across the spectrum of physical illness. It has been a major factor in the reductions in morbidity and mortality that have been achieved in some of the non-communicable diseases, notably cancer and cardiovascular disease. Over the past two decades, an international collaborative effort has been mounted to build the evidence and the capacity for early intervention in the psychotic disorders, notably schizophrenia, where for so long deep pessimism had reigned. The origins and rapid development of early intervention in psychosis are described from a personal and Australian perspective. This uniquely evidence-informed, evidence-building and cost-effective reform provides a blueprint and launch pad to radically change the wider landscape of mental health care and dissolve many of the barriers that have constrained progress for so long.

Key Words: Early intervention, psychosis, prevention, service reform

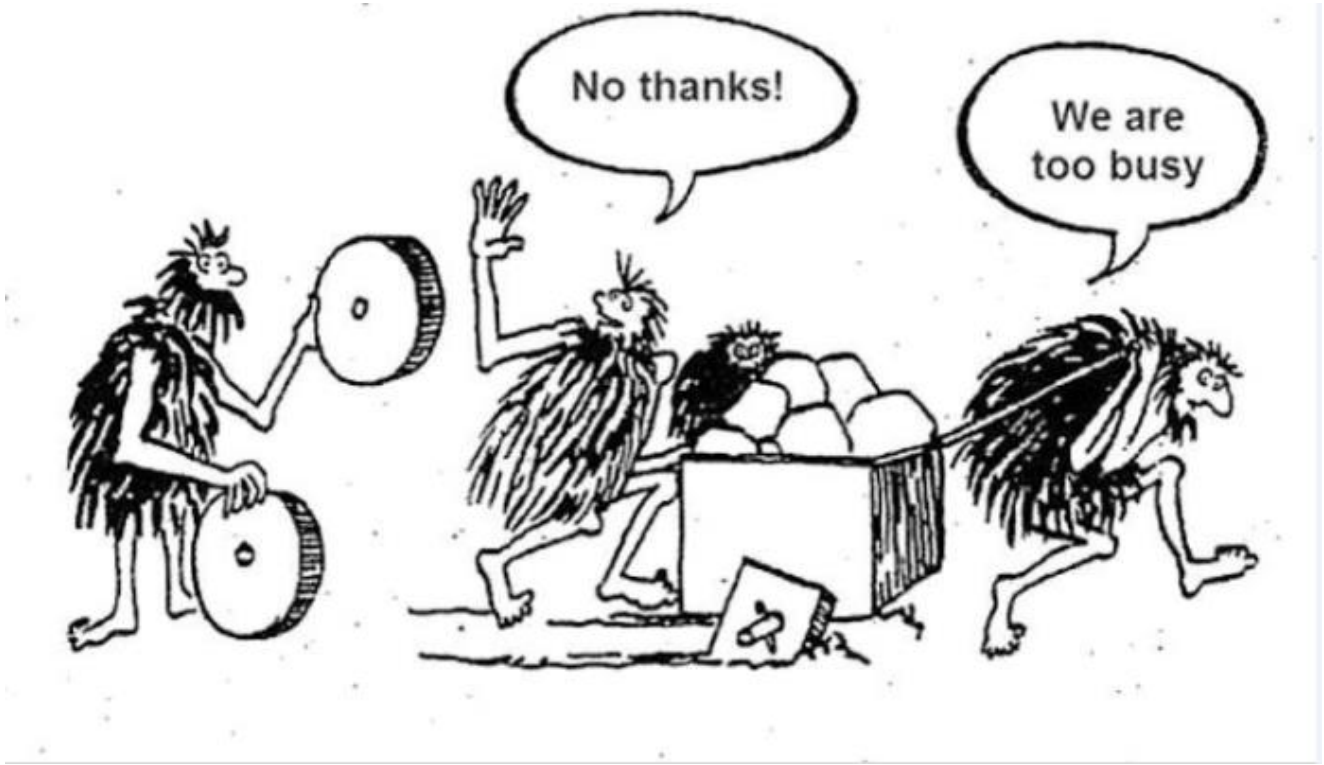
(*J Nerv Ment Dis* 2015;203: 310–318)

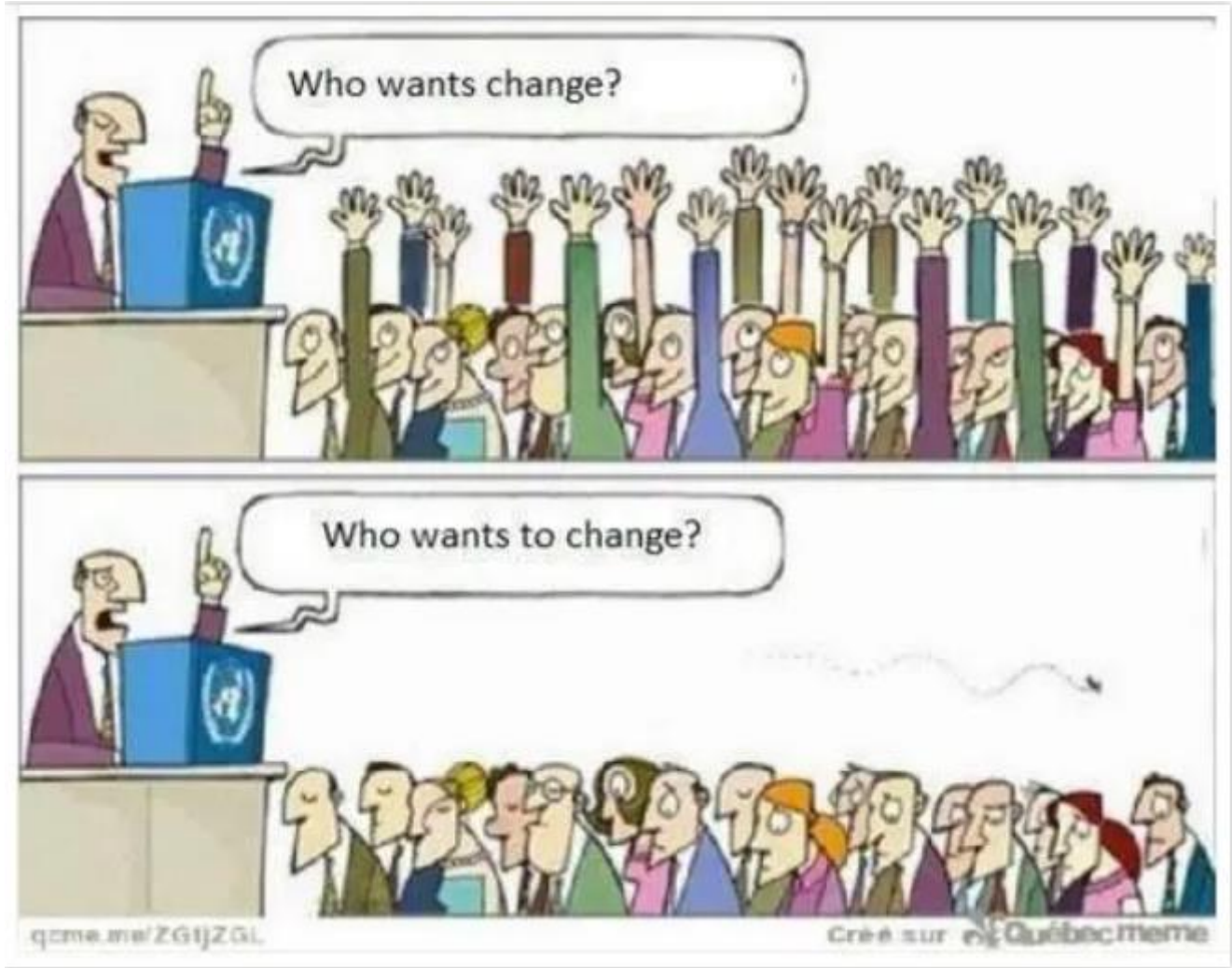
ORIGINS

Mental disorders have always been misunderstood, heavily stigmatized, and until recently, actively hidden from
well-intentioned 19th century attempts to make p
asylum movement and the development of a descri
tem ended up reinforcing these destructive forc
better illustrated than in the phenomenon of dem
schizophrenia, which was deliberately associated c
Kraepelin and his contemporaries with an essenti
Although these were serious illnesses and at the tim
tive treatment, this was a serious conceptual and st
the corrosive pessimism it reinforced was to cloud
of people with psychosis for over a century. There w
to this orthodoxy. For example, the American soci
Stack Sullivan stated: "I feel certain that many inci

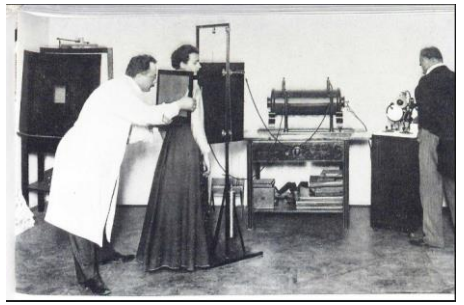


WHY?


No thanks!
We are too busy


Who wants change?
Who wants to change?
qcme.me/ZGtjZGL
Créé sur Quebecmeme

- Should we continue with the psychiatry of yesteryear when we know that new methods are more effective and better accepted by patients?
- Is it the case in other domains of medicine?
- How is it that in psychiatry it is acceptable not to offer patients new approaches that have already proved their worth...?



We need to advocate for our patients to improve their care!

European Psychiatry

www.cambridge.org/epa

Viewpoint

Cite this article: Nordentoft M, Rasmussen M, Høgh L, Legind C, Kjellberg J (2023). How come Denmark is planning to increase the annual budget for psychiatry by almost 20 percent?. *European Psychiatry*, **66**(1), e68, 1–4 https://doi.org/10.1192/j.eurpsy.2023.2409

Received: 20 April 2023
Revised: 30 April 2023
Accepted: 01 May 2023

Keywords:
Psychiatry; public health; burden of disease; mental health services

Corresponding author:
Merete Nordentoft;
Email: mn@dadlnet.dk

EUROPEAN PSYCHIATRIC ASSOCIATION

How come Denmark is planning to increase the annual budget for psychiatry by almost 20 percent?

Merete Nordentoft[1,2,3], Mikkel Rasmussen[3,5], Lene Høgh[3,4], Christian Legind[1,2,3] and Jakob Kjellberg[6]

[1]Mental Health Centre Copenhagen, Mental Health Services in the Capital Region of Denmark, Hellerup, Denmark; [2]Department of Clinical Medicine, Faculty of Health and Medical Science, University of Copenhagen, Copenhagen, Denmark; [3]Danish Psychiatric Society, Copenhagen, Denmark; [4]Central Denmark Region, Aarhus, Denmark; [5]Mental Health Centre Horsens, Mental Health Services in Central Region, Horsens, Denmark and [6]VIVE – The Danish Centre for Social Science Research, Copenhagen, Denmark

Abstract

In Denmark, a 10-year plan for psychiatry has been agreed on. The content of the plan was developed in collaboration between the Danish Health Authority and the Danish Authority for Social Services and Housing, and it involved many stakeholders. Recently, the government presented a planned investment that would increase the overall budget in Danish regions and municipalities by almost 20 percent over a 10-year period. Epidemiological research demonstrating shortened life expectancy and high levels of burden of disease for people with mental disorders contributed to emphasizing the need for improvement of psychiatric services. User organizations, trade unions, and scientific societies in the field of mental health were unified in a common organization, called the Psychiatry Alliance, and this alliance agreed on common action points and acted together to influence politicians. An assertive approach toward politicians and media was pivotal, and being a first mover and presenting tentative budgets was very influential.

Organization of Danish healthcare

Psychiatric treatment in Denmark is organized through a public healthcare system, that is publicly funded and covers the whole population [1]. It is divided into the primary and the secondary healthcare sector. In the primary healthcare sector, all citizens have their own general practitioner, who can provide basic treatment and refer them to private specialists, to social services, or to hospital-based in- and out-patient facilities in the secondary healthcare sector. Secondary healthcare is organized in five Danish regions. Since 2013, psychiatric disorders, with at least moderate severity, are covered by the "right to evaluation and treatment" in the secondary health sector within 30 days. This has led to a 25 percent increase in the number of patients treated in secondary healthcare. The guiding principles for psychiatric healthcare are accessibility, quality, and patient-centered treatment, but a lack of resources can make it difficult to live up to these principles.

Historical view

In Denmark, psychiatry has been a hot topic in the public debate for many years. The previous government (2019 to 2022) decided to initiate a 10-year plan for psychiatry. The content of the plan was developed in collaboration between the Danish Health Authority and the Danish Authority for Social Services and Housing, and it involved many stakeholders [2].

In November 2022, the newly elected government published its policy for its time in office. In it was stated that a substantial investment would be made in the 10-year plan for psychiatry. The government planned to increase the annual expenses by 3 billion Danish krones (DKK), equivalent to 400 million Euros. Since 2019, 1,1 billion DKK have already been allocated for psychiatry annually. Taken together, these investments are equivalent to an approximately 18% increase in the total budget for psychiatry in Danish regions and municipalities.

We are still awaiting the actual investment, and it is therefore too early to get a clear picture of what exact investments are planned. The specific areas of investment are not defined yet, and the release of the majority of funds is awaited.

A range of different initiatives has led to this remarkable decision regarding investments.

- In Denmark, a 10-year plan for psychiatry has been agreed on.
- The content of the plan was developed in collaboration between the Danish Health Authority and the Danish Authority for Social Services and Housing, and it involved many stakeholders.
- User organizations, trade unions, and scientific societies in the field of mental health were unified in a common organization, called the Psychiatry Alliance
- This alliance agreed on common action points and acted together to influence politicians.

- **An assertive approach toward politicians and media was pivotal, and being a first mover and presenting tentative budgets was very influential.**

Societal challenges

EARLY INTERVENTION IN MENTAL HEALTH

Alison Yung

Pat McGorry

Scott Woods

Barnaby Nelson

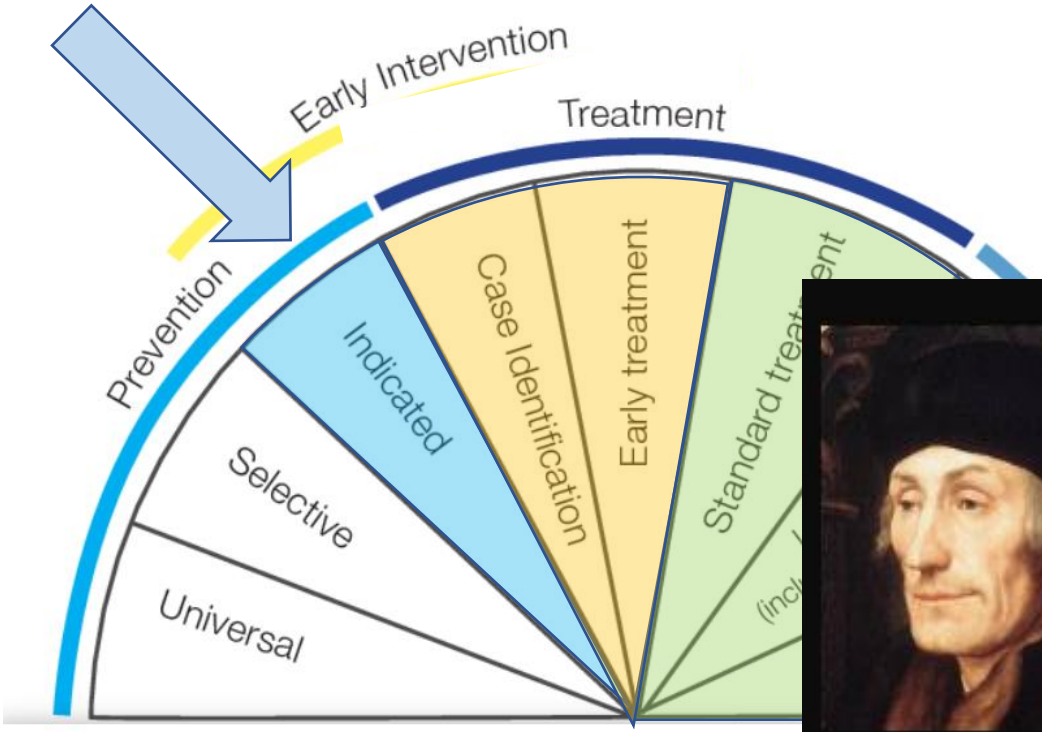
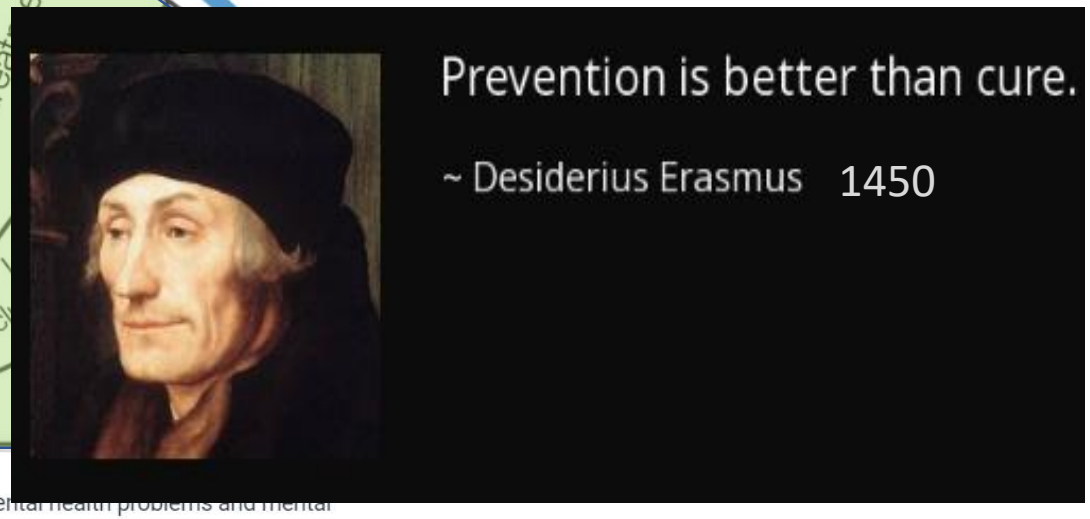


Figure 1: Mrazek & Haggerty's model of the spectrum of interventions for mental health problems and mental disorders50



EARLY INTERVENTION IN MENTAL HEALTH

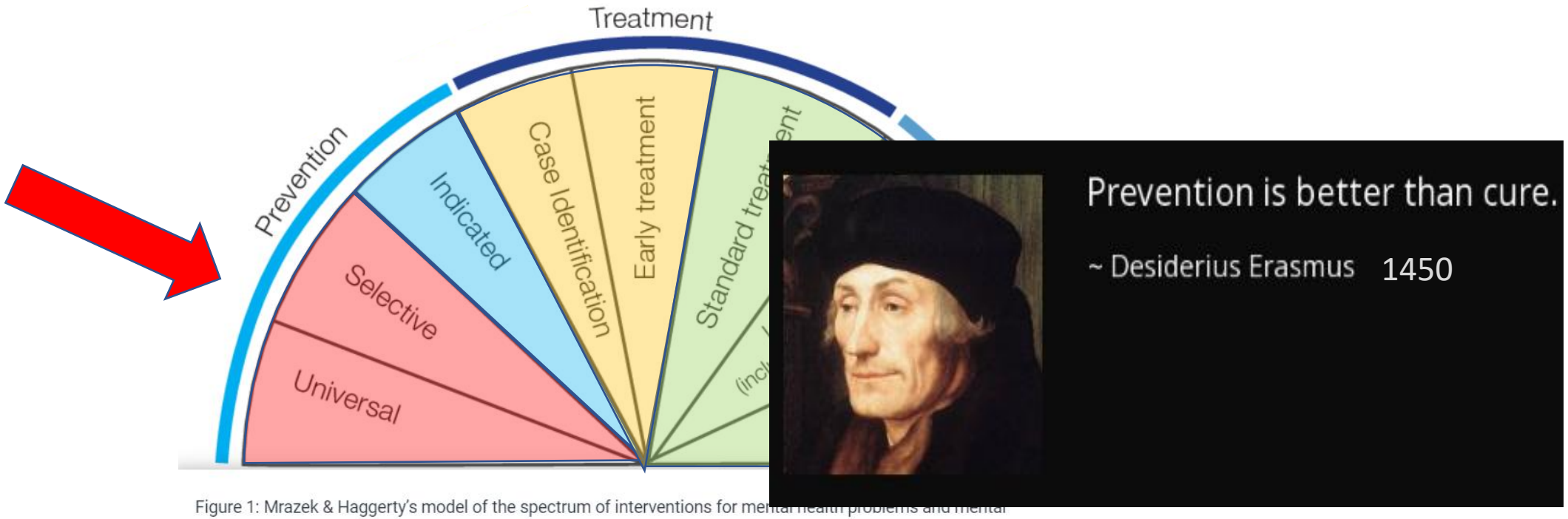


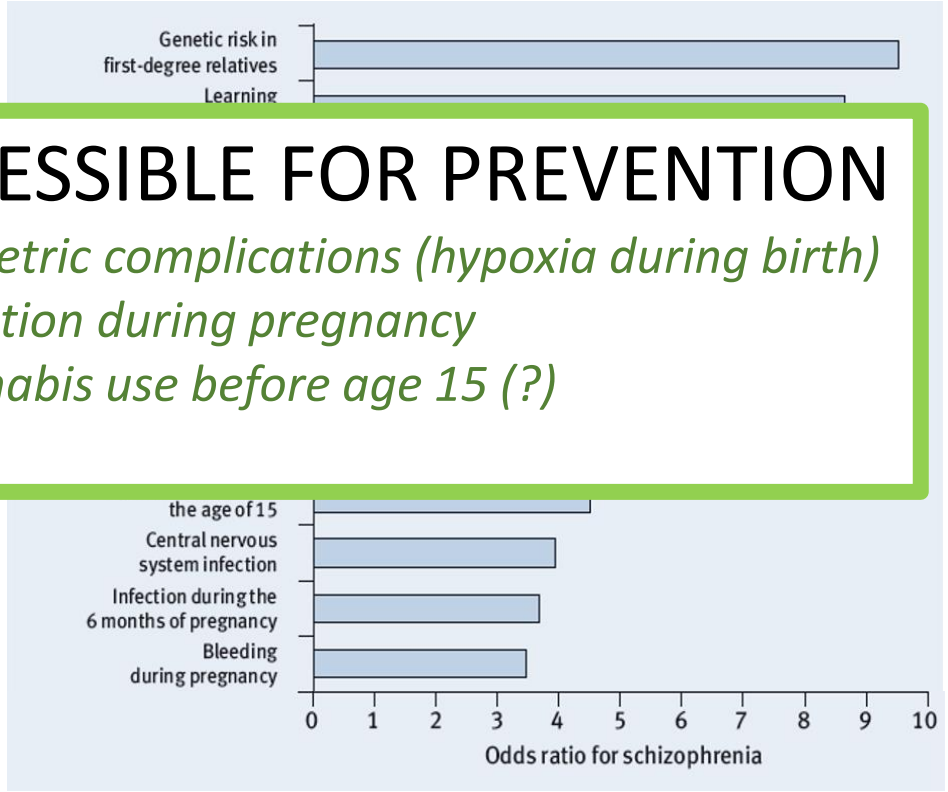
Figure 1: Mrazek & Haggerty's model of the spectrum of interventions for mental health problems and mental disorders50

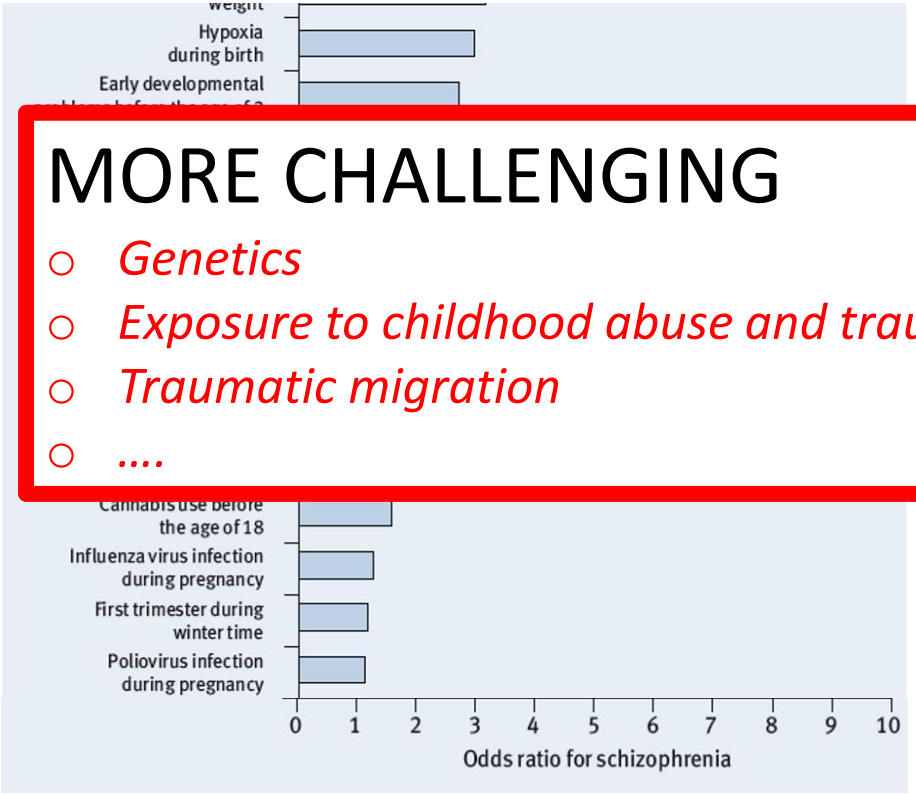
Social and societal déterminants of mental health

- Many papers presented during this conference
- Plenary session of Prof Hanna Kienzler
- Absence of early intervention in low income countries
  - Link with WHO
  - Develop adaptable versions of EI: what are the key éléments?

HAVE WE IDENTIFIED RISK FACTORS ?

The example of schizophrenia





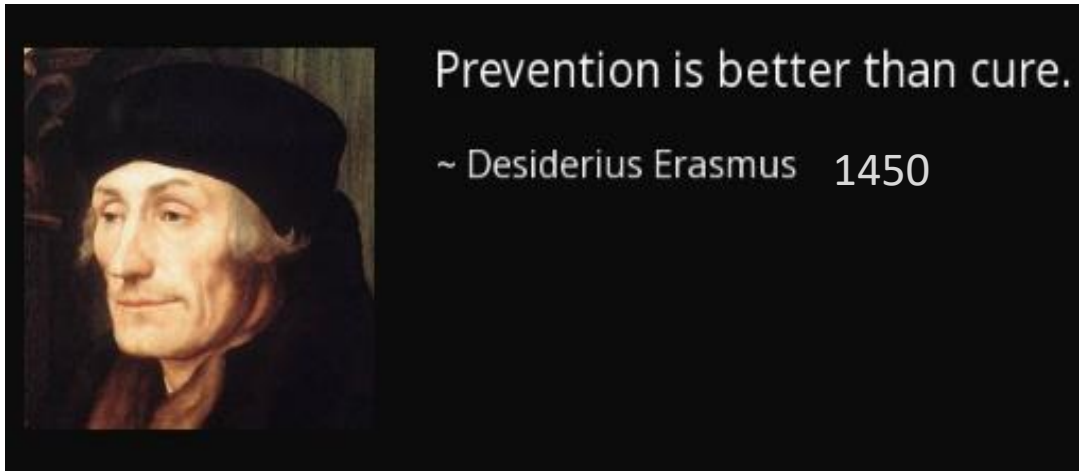
ACCESSIBLE FOR PREVENTION

- ✓ *Obstetric complications (hypoxia during birth)*
- ✓ *Infection during pregnancy*
- ✓ *Cannabis use before age 15 (?)*
- ✓ *….*

MORE CHALLENGING

- *Genetics*
- *Exposure to childhood abuse and trauma*
- *Traumatic migration*
- *….*

Lambert & Naber, Current schizophrenia, Springer 2009



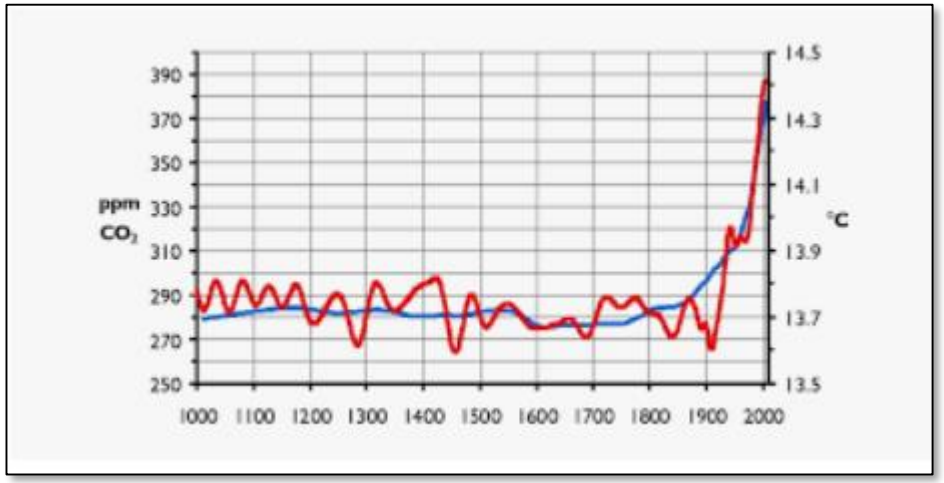
Maybe should we also try and prevent the emergence of new risk factors…?

CLIMATE CHANGE

Climate change: general context

Climate has already changed in the past, but

- *Never as fast*
- *Never with such a direct link with human activity*



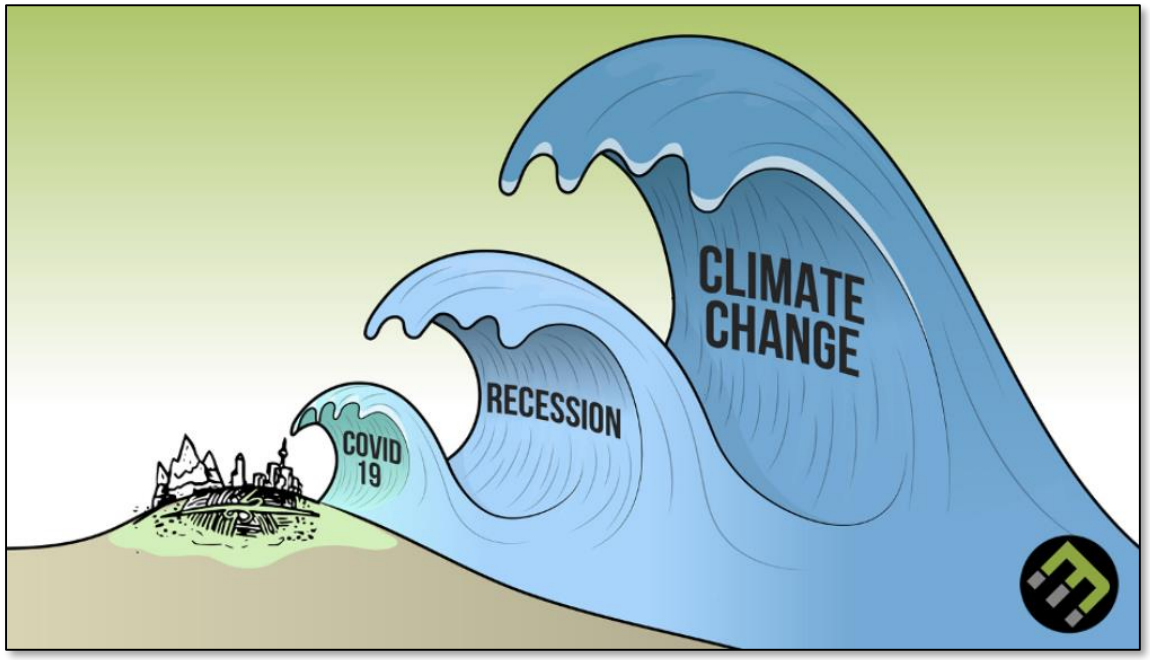
CO2 concentration in the atmosphere

Mean temperature around the world

Climate change: general context

Such changes are linked with

Climate hasards	**Socioeconomic**
Extreme heat	Loss of livelihood
Flood	Property loss or damage
Storm	Loss of autonomy and control
Sea-level rise	Conflict, violence
Drought	Inequalities
Wildfire	Forced migration
	Loss of personal important places



Climate change:
is there a link with mental health?

Empirical evidence of mental health risks posed by climate change

PNAS | October 23, 2018 | vol. 115 | no. 43 | 10953–10958

Nick Obradovich[a,b,1], Robyn Migliorini[c], Martin P. Paulus[d,e], and Iyad Rahwan[a,f]

- ***Hypothesis:*** *Sound mental health may be undermined by climate change.*
- ***Methods:*** *Coupling of meteorological and climatic data with reported mental health difficulties drawn from nearly* ***2 million randomly sampled US residents*** *between 2002 and 2012.*
- ***Results:***
  - ***Shifting from monthly temperatures 25º-30º to >30º*** *increases the probability of mental health difficulties by 0.5% points :* ***2 million more patients for US***
  - ***1ºC of 5-year warming associates with a 2%*** *point increase in the prevalence of mental health issues (id.* ***8 million more patients in the US)***
  - ***Exposure to Hurricane Katrina associates with a 4% point*** *increase in this metric*
- *Conclusion: environmental stressors produced by climate change pose threats to human mental health.*

What is the concrete impact on mental health?

Direct impact: natural disasters

- 40x more psychological than physical disorders
  - PTSD
  - Depression
  - Suicide

Impact of heat waves:

ENVIRONMENTAL HEALTH

Schizophrenia pinpointed as a key factor in heat deaths

The mental illness tripled the risk of death during a searing 2021 heat wave, researchers find

SCIENCE science.org 17 MARCH 2023 • VOL 379 ISSUE 6637 1079

What is the concrete impact on mental health?

Direct impact: natural disasters

- 40x more psychological the physical disorders
  - PTSD
  - Depression
  - Suicide

Gradual impact:

- Slower pace of change (farmers, insular populations…)
- Loss of income and identity
  - Depression, anxiety
  - Suicide

Indirect impact:

- Solastalgia
- Eco-anxiety

Ecoanxiety

- All emotions linked to the feeling of fatality in the face of climate change
- Mainly fear, sadness and anger
- The main cause of this anguish: inaction or insufficient action on climate by governments and populations.

- The Lancet Planetary Health (Lancet 2021; Marks et al.) : **Young people's voices on climate anxiety, government betrayal and moral injury: A global phenomenon**.
  - Method: survey of 10,000 young people aged 16 to 25 in ten different countries.
  - Results:
    - 84% are "worried" about the state of the planet (more than in older populations)
    - 59% are "very worried".
    - >50% feel anxious, sad and angry about the climate crisis
    - 39% hesitate to have children

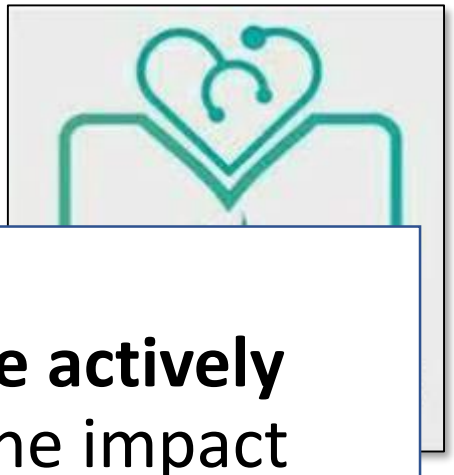
1929 students UNIL
80% worried
60% very worried
72% sad, anxious, angry
55% hesitate having children

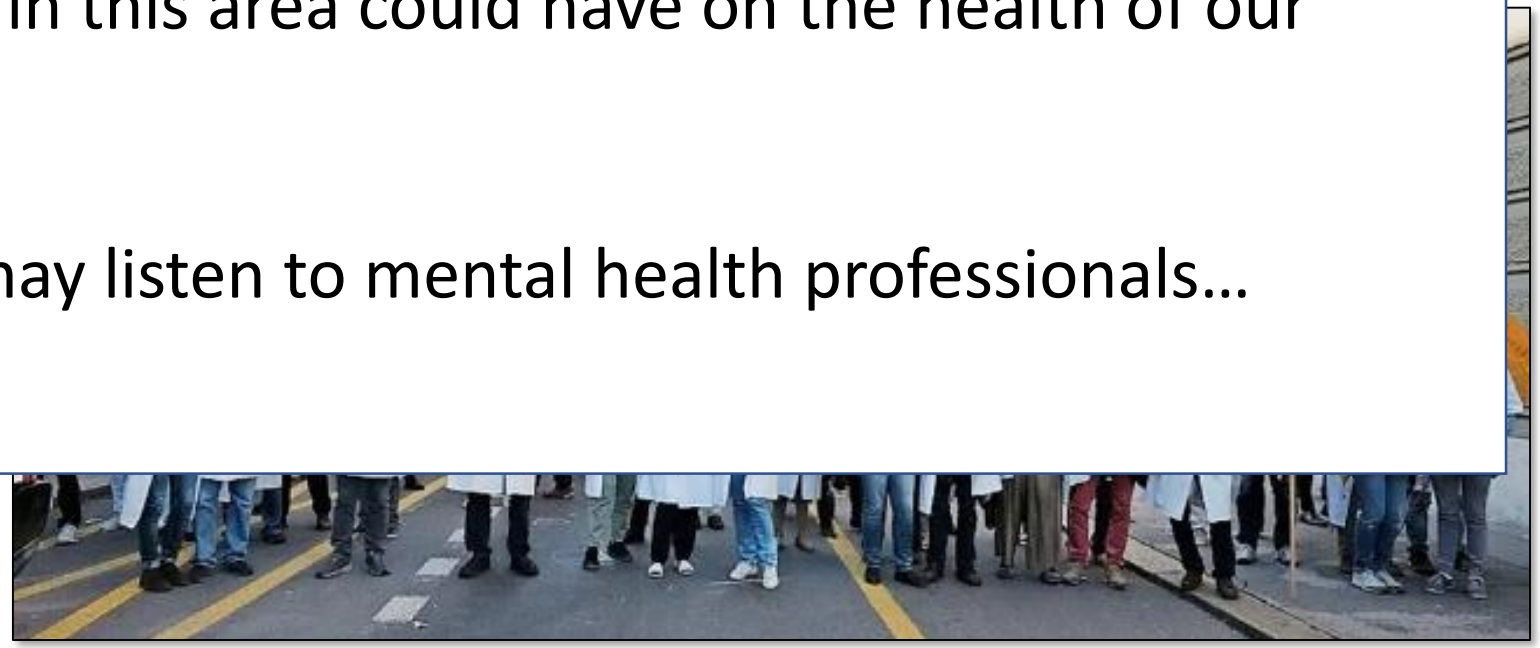
Fouvy, Golay et al.

ECO-ANXIETY:
Pathology or normal reaction?

WHAT CAN WE DO AGAINST CLIMATE CHANGE?

1. Act as individuals
2. Act as citizens
3. Act as health professionals/scientists





- **It is urgent that phyiscians and scientists become actively involved in alerting political authorities** about the impact that inaction in this area could have on the health of our populations

- Authorities may listen to mental health professionals…

Sign the petition launched at IEPA 14 in Lausanne

ACTIONS FOR IEPA now and in the future:

- *No paper program book*
- *Online abstract book*
- *Hybrid conferences*
- *Publication of papers in EIP*
- *Development of an interest group on this topic*
- *….*

Acting against climate change:
A strategy for universal prevention in mental health!

CONCLUSION

- Early intervention in mental health has been a major driver of change in the approach of mental health disorders
- The major focus has been psychosis where much remains to be done
- These strategies need to be applied to other disorders
- True tanslational research is a necessary domain of investment in order to make progress
- Science is not enough: we need to be active politically regarding
  - Right of patients for better care
  - Climate change which is a major threat to mental health around the world

Thank you for your attention
&
FOR YOUR FUTURE ACTIONS!