Università di Cagliari
Dipartimento di Sanità Pubblica, Medicina
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Il trattamento a lungo termine della schizofrenia: dall'early intervention alla recovery

Bernardo Carpiniello

- La schizofrenia: una malattia progressiva e ad alti costi

I costi tangibili e intangibili della schizofrenia

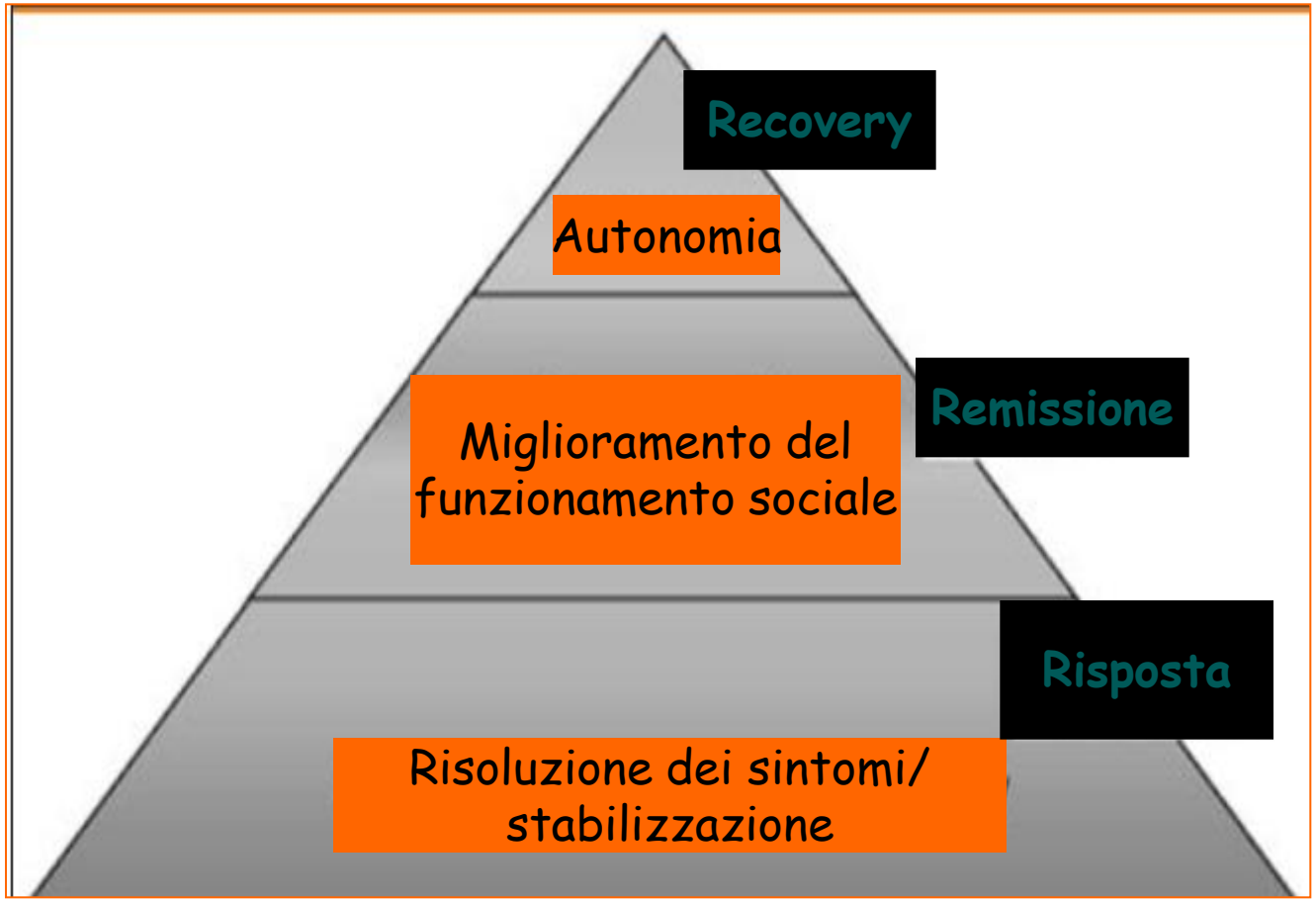
Tasso di mortalità 2.58 superiore a quello della popolazione generale (1)

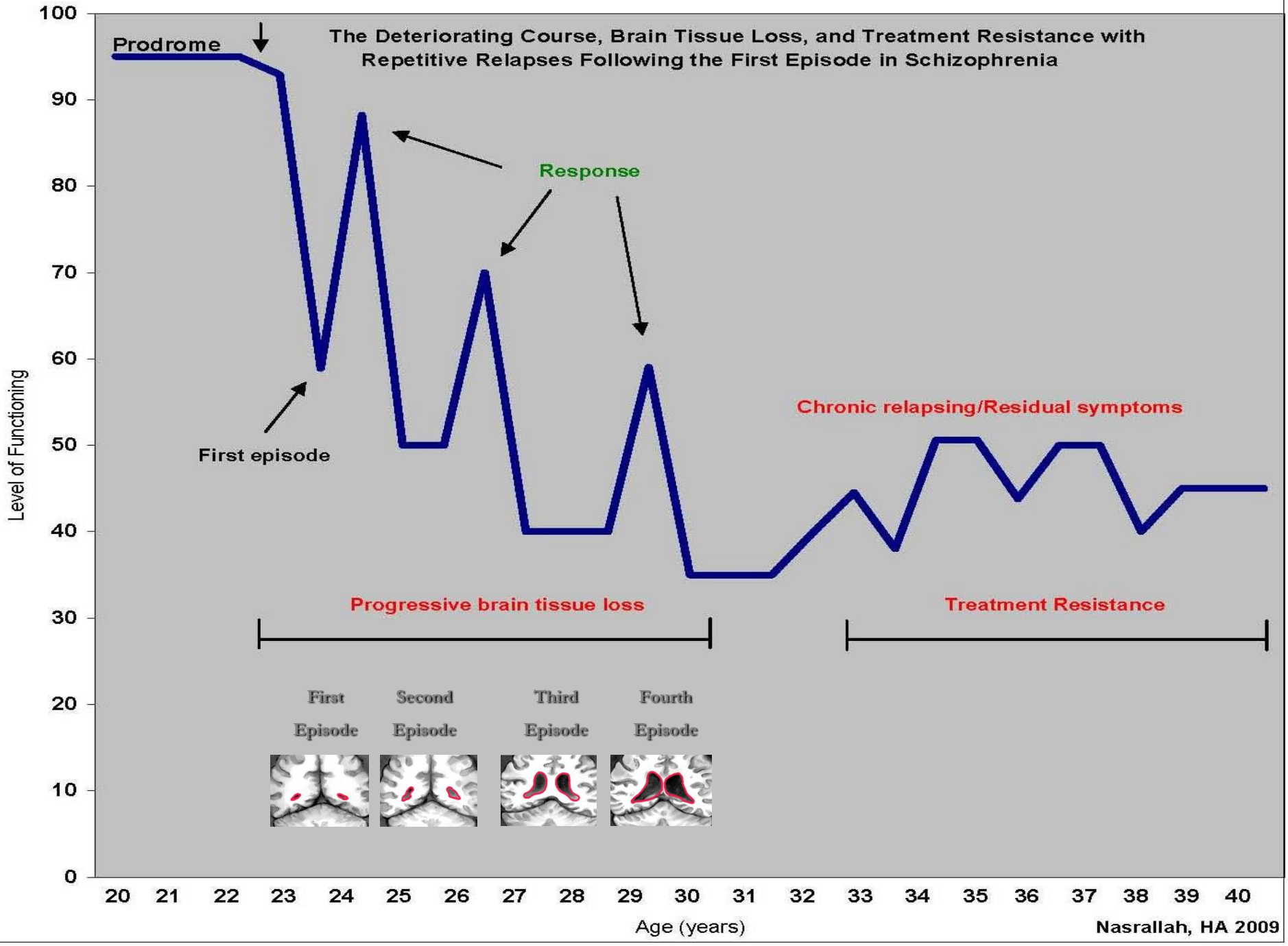
Costi stimati in circa 94 miliardi di € in Europa per:

- Ospedalizzazione e residenzialità
- Perdita di capacità di istruzione e di lavoro
- Stigma, emarginazione
- Comorbidità mediche
- Carico familiare
- Abuso di sostanze

1. Saha S, et al. Arch Gen Psychiatry. 2007; 64:1123-31.

Obiettivi dei trattamenti nella schizofrenia




The Deteriorating Course, Brain Tissue Loss, and Treatment Resistance with Repetitive Relapses Following the First Episode in Schizophrenia
Prodrome
Response
First episode
Chronic relapsing/Residual symptoms
Progressive brain tissue loss
Treatment Resistance
First Episode
Second Episode
Third Episode
Fourth Episode
Level of Functioning
Age (years)
Nasrallah, HA 2009

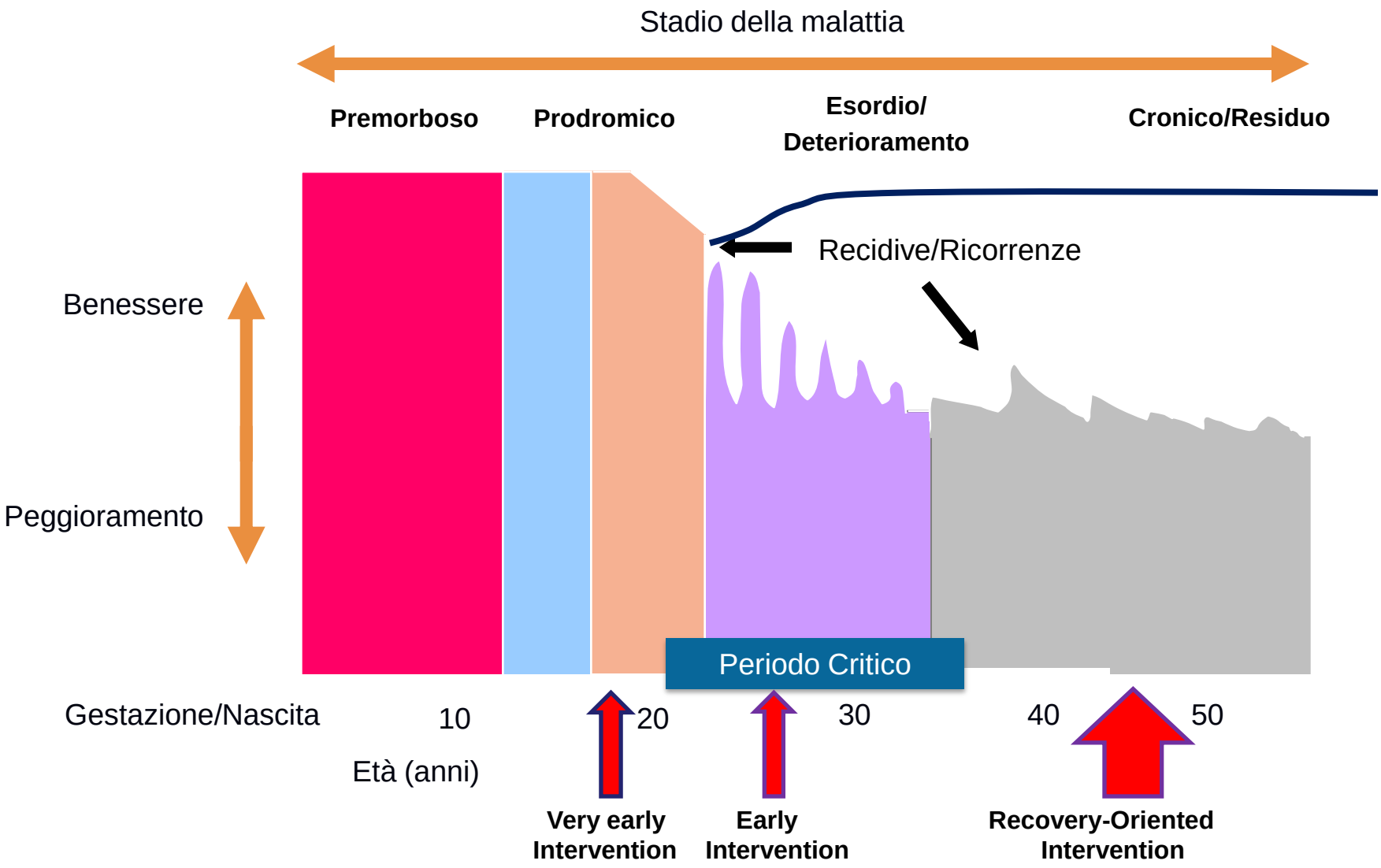
Is psychosis neurotoxic?

"*Acutely active psychosis is a dangerous mental state, if not a medical emergency, because of its aberrant experiences,loss of insight, and distortions of judgment. It requires immediate treatment, including antipsychotic medication, to reduce the danger of such distortions to life and social network. The threat of chronically active psychosis is time rather than mortality and stigma, time immersed in the negative symptoms or cognitive distortions of disorder. If prolonged, it may well create deficits that add to severity beyond the level ultimately determined by the original brain pathophysiology.* ***Whether these further deficits result from brain-damaging neurotoxicity or from attenuated synaptic plasticity secondary to withdrawal from daily commerce is the question posed here. The evidence thus far appears to point to the latter explanation and to endorsing treatment strategies that try first to minimize psychotic distortions*** *with asylum and medication and then to maximize reengagement with reality via outreach strategies and medications that together preserve salience and promote real world investment"*

McGlashan MT, Is active psychosis neurotoxic? Schizophr Bull, 2006,32:609-13

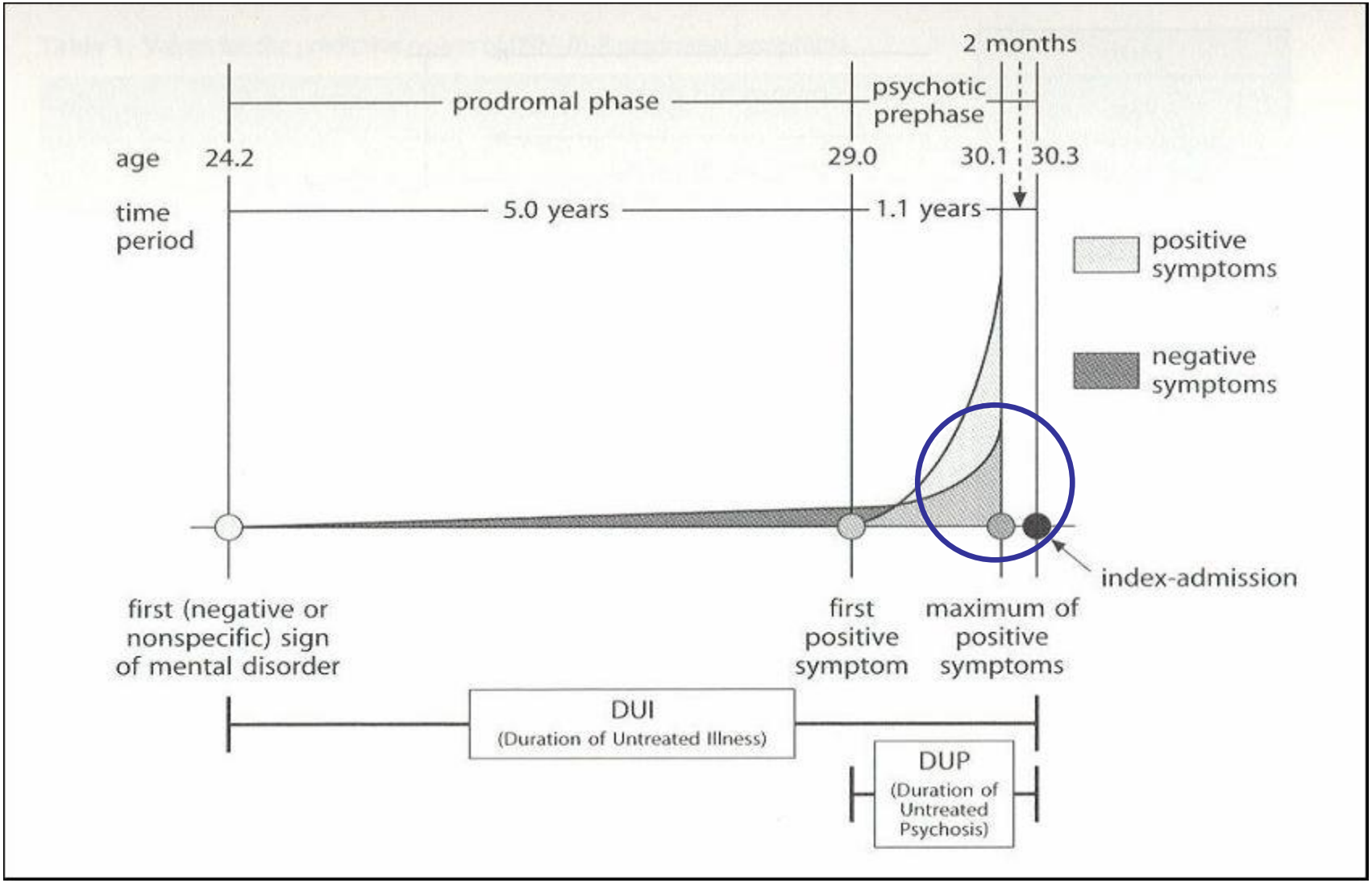
- L’importanza di un intervento precoce, orientato al recovery

Staged Interventions in Schizophrenia



Mod. da Lieberman JA

Duration of Untreated illness and Duration of Untreated Psychosis



Klosterkötter, 2002

Factors characterizing access and latency to first pharmacological treatment in Italian patients with schizophrenia, mood, and anxiety spectrum disorders

Bernardo Dell'Osso[a], Laura Cremaschi[a], Carlotta Palazzo[a], Neva Suardi[a], Gregorio Spagnolin[a], Giulia Camuri[a], Beatrice Benatti[a], Lucio Oldani[a], Cristina Dobrea[a], Chiara Arici[a], Giovanna Pace[a], Alessandra Tiseo[a], Ester Sembira Nahum[a], Filippo Castellano[b], Nazario D'Urso[b], Massimo Clerici[b], Diego Primavera[c], Bernardo Carpiniello[c] and A. Carlo Altamura[a]

Latency to first pharmacological treatment [duration of untreated illness (DUI)] in psychiatric disorders can be measured in years, with differences across diagnostic areas and relevant consequences in terms of socio-occupational functioning and outcome. Within the psychopathological onset of a specific disorder, many factors influence access and latency to first pharmacotherapy and the present study aimed to investigate such factors, through an ad-hoc developed questionnaire, in a sample of 538 patients with diagnoses of schizophrenia-spectrum disorder (SZ), mood disorder (MD), and anxiety disorder (AD). Patients with SZs showed earlier ages at onset, first diagnosis and treatment, as well as shorter DUI compared with other patients (43.17 months vs. 58.64 and 80.43 months in MD and AD; $F = 3.813$, $P = 0.02$). Patients with MD and AD reported more frequently onset-related stressful events, benzodiazepines as first treatment, and autonomous help seeking compared with patients with SZs. In terms of first therapist, psychiatrist referral accounted for 43.6% of the cases, progressively decreasing from SZ to MD and AD (57.6, 41.8, and 38.3%, respectively). The opposite phenomenon was observed for nonpsychiatrist clinician referrals, whereas psychologist referrals remained constant. The present findings confirm the presence of a relevant DUI in a large sample of Italian patients with different psychiatric disorders (5 years, on average), pointing out specific differences, in terms of treatment access and latency, between psychotic and affective patients. Such aspects are relevant for detection of at-risk patients and implement early intervention programs. *Int Clin Psychopharmacol* **00:000–000**

International Clinical Psychopharmacology 2014, **00**:000–000

Keywords: anxiety disorders, duration of untreated illness, latency to treatment, mood disorders, schizophrenia-spectrum disorders

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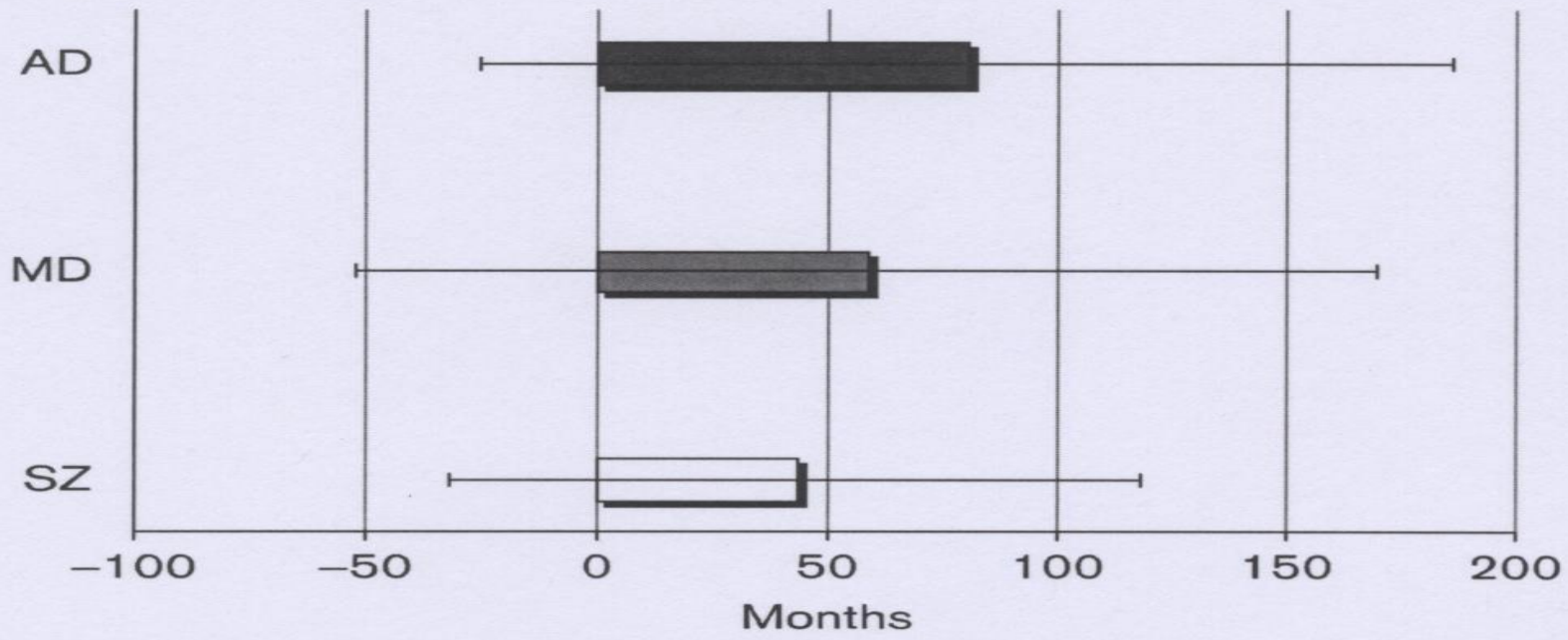
Fig. 1



Differences in terms of DUI among diagnostic subgroups (SZ, MD, and AD). AD, anxiety disorders [panic disorder (PD), generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD)]; DUI, duration of untreated illness; MD, mood disorders [major depressive disorder (MDD), bipolar disorder (BD)]; SZ, schizophrenia spectrum disorders (delusional disorder, schizoaffective disorder, schizophreniform disorder, schizophrenia) ($F = 3.83$, $P = 0.022$).

ANNALS OF GENERAL PSYCHIATRY

PRIMARY RESEARCH Open Access

Does duration of untreated psychosis predict very long term outcome of schizophrenic disorders? results of a retrospective study

Diego Primavera[1], Chiara Bandecchi[1], Tiziana Lepori[1], Lucia Sanna[1], Eraldo Nicotra[2] and Bernardo Carpiniello[1,3*]

Abstract

Background: Studies performed to assess the relevance of duration of untreated psychosis (DUP) as a predictor of long-term outcome (i.e. follow-ups of ten years or more) are somewhat limited. The aim of this study was to evaluate the potential association between DUP and very long-term outcome (16-33 yrs) of schizophrenia by means of a retrospective design.

Methods: Retrospective data obtained from clinical records were collected regarding DUP and outcome variables (number of hospitalizations; number of attempted suicides; course of illness; GAF scores at last observation) for a cohort of 80 outpatients (52 Males, 28 Females, mean age 51.0+/-11.58 years) affected by schizophrenia according to DSMIVTR attending a university community mental health centre.

Results: Mean duration of follow up was 25.2 +/- 8.68 years; mean duration of untreated psychosis was 49.00 months (range 1-312 mo), with no significant difference according to gender. Patients with a shorter DUP (=/< 1 year) displayed more frequent "favourable" courses of illness (28.9% vs 8.6%) ($p = 0.025$), more frequent cases with limited (=/< 3) number of hospital admissions (85.7% vs 62.1%) ($p = 0.047$) and a better functioning (mean GAF score = 50.32+/-16.49 vs 40.26+/-9.60, $p = 0.002$); regression analyses confirmed that shorter DUP independently predicted a more positive outcome in terms of number of hospital admissions, course of illness, functioning (GAF scores).

Conclusion: A shorter DUP appears to act as a significant predictor of better outcome in schizophrenia even in the very long-term.

Odds of No remission in FEP patients: Long vs Short DUP

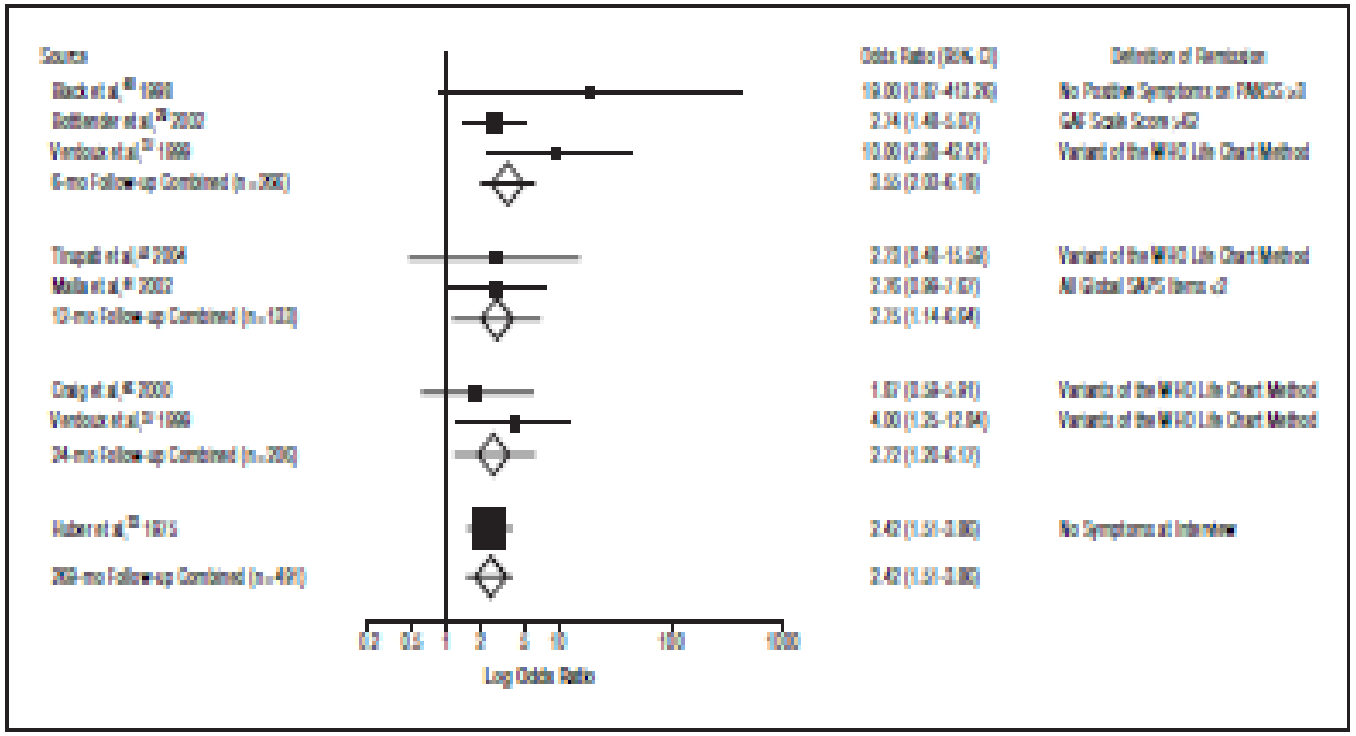


Figure 2. Odds of no remission in the long vs short duration of untreated psychosis (DUP) groups. An odds ratio greater than 1 indicates that individuals in the long DUP group were more likely not to be in remission at the follow-up point. CI indicates confidence interval; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; WHO, World Health Organization; and SAPS, Scale for the Assessment of Positive Symptoms. Squares indicate the size of the contribution to the study of the summary odds ratio (diamonds).

From: Marshall et al, Association between duration of untreated psychosis and Outcome in cohorts of first-episode patients.A systematic review, Arch Gen Psych, 2005,62:975-83

BJPsych | The British Journal of Psychiatry (2014)
205, 88–94. doi: 10.1192/bjp.bp.113.127753

Review article

Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis†

Matti Penttilä, Erika Jääskeläinen, Noora Hirvonen, Matti Isohanni and Jouko Miettunen

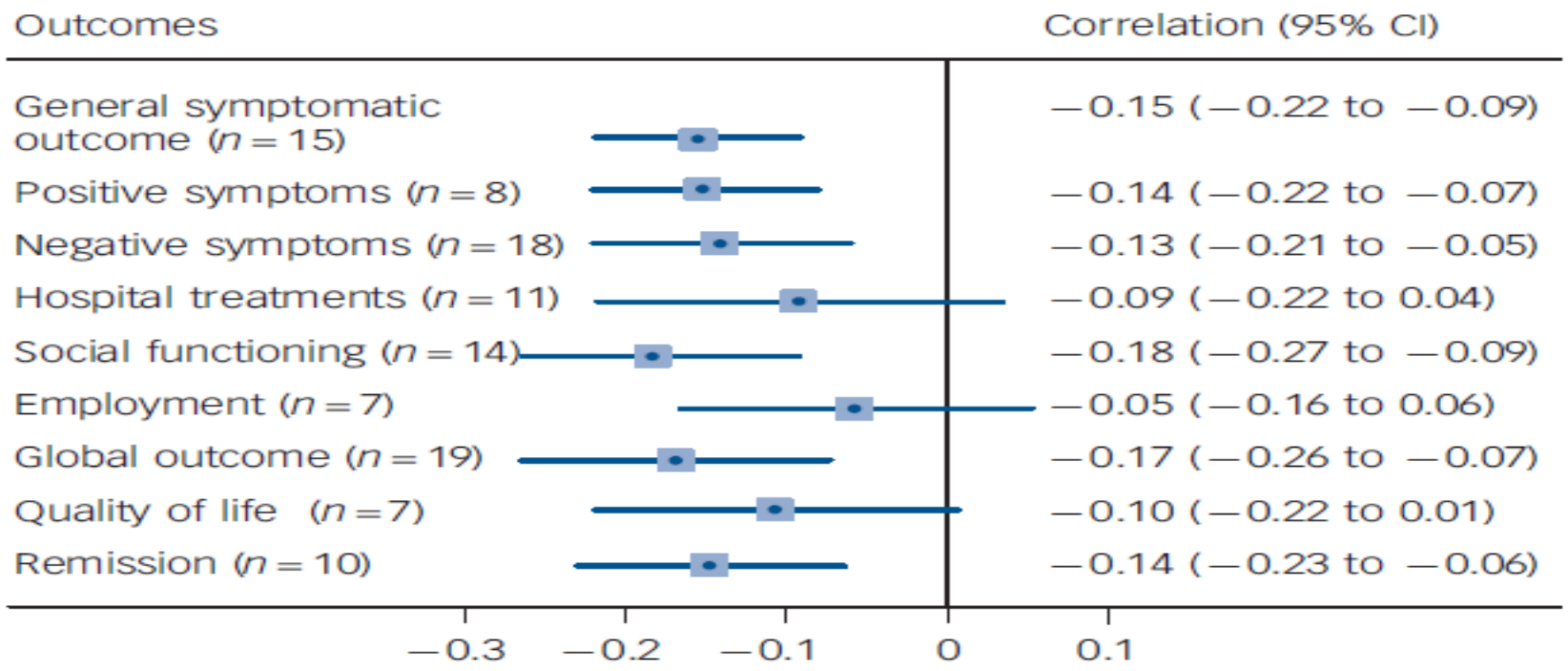
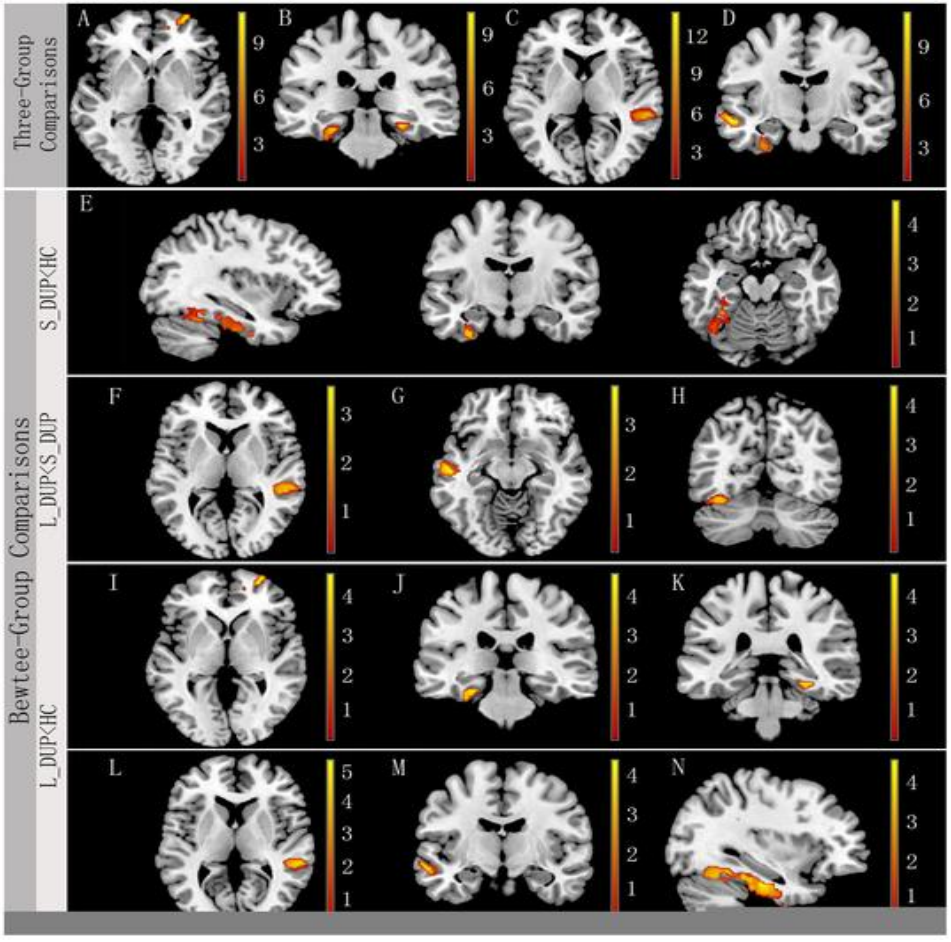


Fig. 2 Correlations between duration of untreated psychosis (DUP) and clinical outcomes, hospital treatment and social functioning. Negative correlation indicates that long DUP is associated with poor outcome (*n*, number of studies).

- **Brain anatomical regions that showed significant difference in gray matter volume among the three groups (right is right).**



RESULTS: Fifty-seven patients (27 short **DUP** and 30 **long DUP**) and 30 healthy controls were included in the analysis. There were significant gray matter volumetric differences among the 3 groups in bilateral parahippocampus gyri, right superior temporal gyrus, left fusiform gyrus, left middle temporal gyrus, and right superior frontal gyrus (p's<0.01). Compared with healthy controls, the **long DUP** group had significantly smaller volume in all these regions (p's <0.05). Compared with the short-**DUP** group, the **long-DUP** group had significantly smaller volume in right superior temporal gyrus, left fusiform gyrus, and left middle temporal gyrus (p's<0.01).

CONCLUSION: Our findings suggest that **DUP** is associated with temporal and occipitotemporal gray matter volume decrease in treatment naïve schizophrenia. The brain structural changes in **untreated psychosis** might contribute to poor treatment response and **long-term** prognosis in this patient population.

Guo X, Li J, Wei Q, Fan X, et al. (2013) Duration of Untreated Psychosis Is Associated with Temporal and Occipitotemporal Gray Matter Volume Decrease in Treatment Naïve Schizophrenia. PLoS ONE 8(12): e83679. doi:10.1371/journal.pone.0083679
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0083679

PLOS | ONE

- L’early intervention: modelli, risultati

Early Intervention in Psychosis

Obvious, Effective, Overdue

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

Prevention has played a role in reducing the incidence of cardiovascular disease and some cancers, and some new therapeutic strategies have emerged recently; however, early diagnosis and the sustained and sophisticated delivery of existing therapies have been the decisive factors in improving outcomes. Yet across the world, even in the most developed countries, only a small minority of people with mental illness obtain access to evidence-based care, and even then, typically only after prolonged delays (Organization for Economic Co-operation and Development, 2014). The human and economic consequences of this neglect are enormous (Bloom et al., 2011), especially because mental disorders largely begin in young people on the threshold of productive life (Insel and Fenton, 2005). However, the opportunity to save lives, restore and safeguard futures, and strengthen the global economy are equally huge and beckoning (The Economist, 2014). The evidence-based reform of early intervention in psychosis represents a blueprint and launch pad to radically change the landscape and dissolve many of the barriers that have constrained effective mental health care for so long.

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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 process of schizophrenia and related disorders appears to be most powerful at the onset and early in its manifest course, and this constitutes the rationale for stating that the most intensive and qualified intervention should be started as early as possible. The early phases of psychosis, including long periods of untreated psychosis, are associated with the highest risks of complications, such as loss of contact with family and friends [ ], suicidal acts [ ], development of comorbid substance use and criminality [ ]. 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 [ ] which leads to high levels of family burden [ ].

Curr Opin Psychiatry 2014, 27:167–172

Modelli di intervento per il trattamento dei FEP

- Modello dei Servizi Super-specialistici (Early Intervention services)

- Modello del Servizio Specializzato Centralizzato con diramazioni periferiche (Hub and spoke model)

- Modello dei servizi generalisti «competenti»

Early Intervention in Psychosis

Obvious, Effective, Overdue

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

TABLE 1. The Core Components of a Specialized Early Psychosis Service

Early detection

- Component 1: *Community education* to improve awareness of young people's mental health issues among the general public and those who work closely with young people
- Component 2: *Easy access to the service* through one clear entry point with a "no wrong door" policy and guaranteed referral for those who do not meet entry criteria
- Component 3: *Home-based assessment and care* available via a mobile multidisciplinary team able to provide triage, assessment, crisis intervention, and home-based acute treatment 24 hrs a day, 7 days a week

Acute care

- Component 4: *Acute phase care* delivered in the community by the mobile team, or when necessary, in a dedicated youth-friendly inpatient unit
- Component 5: *Access to subacute care* for additional support after an acute episode

Continuing care

- Component 6: *Case management* with an individual case manager who provides an individually tailored treatment approach as well as support with practical issues
- Component 7: *Medical interventions*, primarily low-dose pharmacotherapy
- Component 8: *Psychological interventions*, including psychoeducation, individual psychotherapy, and cognitive behavioural therapy
- Component 9: *A functional recovery program* with an emphasis on returning to full social, educational, and vocational functioning
- Component 10: *Group programs* to enhance psychosocial and functional recovery. The focus should be on topics of interest to young people, ranging from health-related issues, such as stress management, coping with anxiety and reducing drug use, to study, school, and work issues, as well as social and leisure activities such as music, art, and outdoor adventure
- Component 11: *Family programs and family peer support* for the families and friends of young people with early psychosis
- Component 12: *Youth participation and peer support* is crucial for maintaining youth-friendliness and accountability to young people in these services
- Component 13: *Mobile outreach* for those young people with complex issues who have difficulty engaging with services
- Component 14: *Partnerships* with other organizations that can enhance the support for young people with mental health issues
- Component 15: *Workforce development* to create highly skilled and clinically expert mental health professionals specializing in youth mental health
- Component 16: *Ultra-high risk young people* should be treated within a specialized service with the aim of minimizing symptoms and distress and maintaining a normal functional trajectory to prevent further deterioration in functioning to prevent a first episode of psychosis

These can be loosely grouped according to their function within the service, with certain components operating across the whole model, whereas others are more closely aligned to one of the three key functions of early detection, acute care, and recovery. This allows for a flexible, yet comprehensive, service that is able to respond quickly and appropriately to the individual needs of the young person and their family.

Early intervention services, cognitive–behavioural therapy and family intervention in early psychosis: systematic review

V. Bird, P. Premkumar, T. Kendall, C. Whittington, J. Mitchell and E. Kuipers

Table 2 Analysis of interventions for early psychosis compared with standard care (random-effects model)

Outcome	Time of data collection	Trials, *n*	Participants, *n*: treatment/control	Summary effect estimate (95% CI)
Early intervention service				
Hospital admission[11,12,24]	End of treatment	3	342/280	RR = 0.67 (0.54 to 0.83)
Relapse (full or partial)[11,12]	End of treatment	2	91/81	RR = 0.66 (0.47 to 0.94)
Positive symptoms (PANSS or SAPS) [11,24]	End of treatment	2	260/208	SMD = −0.21 (−0.42 to −0.01)
Negative symptoms (PANSS or SANS)[11,24]	End of treatment	2	260/208	SMD = −0.39 (−0.57 to −0.20)
Not receiving a psychological intervention[11,12,24]	End of treatment	3	344/286	RR = 0.67 (0.46 to 0.97)
Not in contact with index team[11,24]	End of treatment	2	314/266	RR = 0.60 (0.39 to 0.92)
Leaving the study early for any reason[11,12,23,24]	End of treatment	4	408/392	RR = 0.71 (0.53 to 0.94)
Cognitive–behavioural therapy				
Positive symptoms (BRPS, PANSS or SAPS)[25–28]	End of treatment	4	285/251	SMD = −0.05 (−0.22 to 0.12)
Positive symptoms[26–28]	Up to 2 years follow-up	3	233/209	SMD = −0.60 (−0.79 to −0.41)
Negative symptoms (BRPS, PANSS or SAPS)[25,27,28]	End of treatment	3	207/191	SMD = 0.03 (−0.17 to 0.23)
Negative symptoms[26–28]	Up to 2 years follow-up	3	233/209	SMD = −0.45 (−0.80 to −0.09)
Relapse[26,27]	Up to 2 years follow-up	2	227/227	RR = 0.67 (0.24 to 1.85)
Hospital admission[25,26]	Up to 2 years follow-up	2	146/148	RR = 1.01 (0.76 to 1.35)
Family intervention				
Relapse[29]	End of treatment	1	52/52	RR = 0.58 (0.25 to 1.36)
Relapse[29]	Up to 2 years follow-up	1	52/52	RR = 0.75 (0.39 to 1.43)
Hospital admission[30,31]	End of treatment	2	99/90	RR = 0.51 (0.24 to 1.10)
Hospital admission and relapse (combined)[29–31]	End of treatment	3	151/142	RR = 0.50 (0.32 to 0.80)

BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale; RR, relative risk; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SMD, standardised mean difference.

BJPsych | The British Journal of Psychiatry (2010) 197, 350–356. doi: 10.1192/bjp.bp.109.074526

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

Table 1. Clinical outcome and user satisfaction of patients with a first episode of psychotic illness who received intensive early intervention program (OPUS) or standard treatment

	Two-year follow-up N = 369				
	OPUS (N = 205)	Standard treatment (N = 164)	Estimated mean difference (95% CI)	P value of difference	Cohen's d
Psychotic dimension	1.06 (1.26)	1.27 (1.40)	−0.32 (−0.58 to − 0.06)	0.02	0.16
Negative dimension	1.41 (1.15)	1.82 (1.23)	−0.45 (−0.67 to −0.22)	<0.001	0.34
Disorganized dimension	0.37 (0.56)	0.50 (0.73)	−0.12 (−0.25 to −0.00)	0.06	0.20
GAF symptoms	51.18 (15.01)	48.67 (15.92)	2.45 (−0.32 to 5.22)	0.08	0.16
GAF function	55.16 (15.15)	51.13 (15.92)	3.12 (0.37 to 5.88)	0.03	0.26
User satisfaction	26.1 (3.7)	22.9 (5.2)	3.09 (2.10 to 4.04)	<0.001	0.67

CURRENT OPINION

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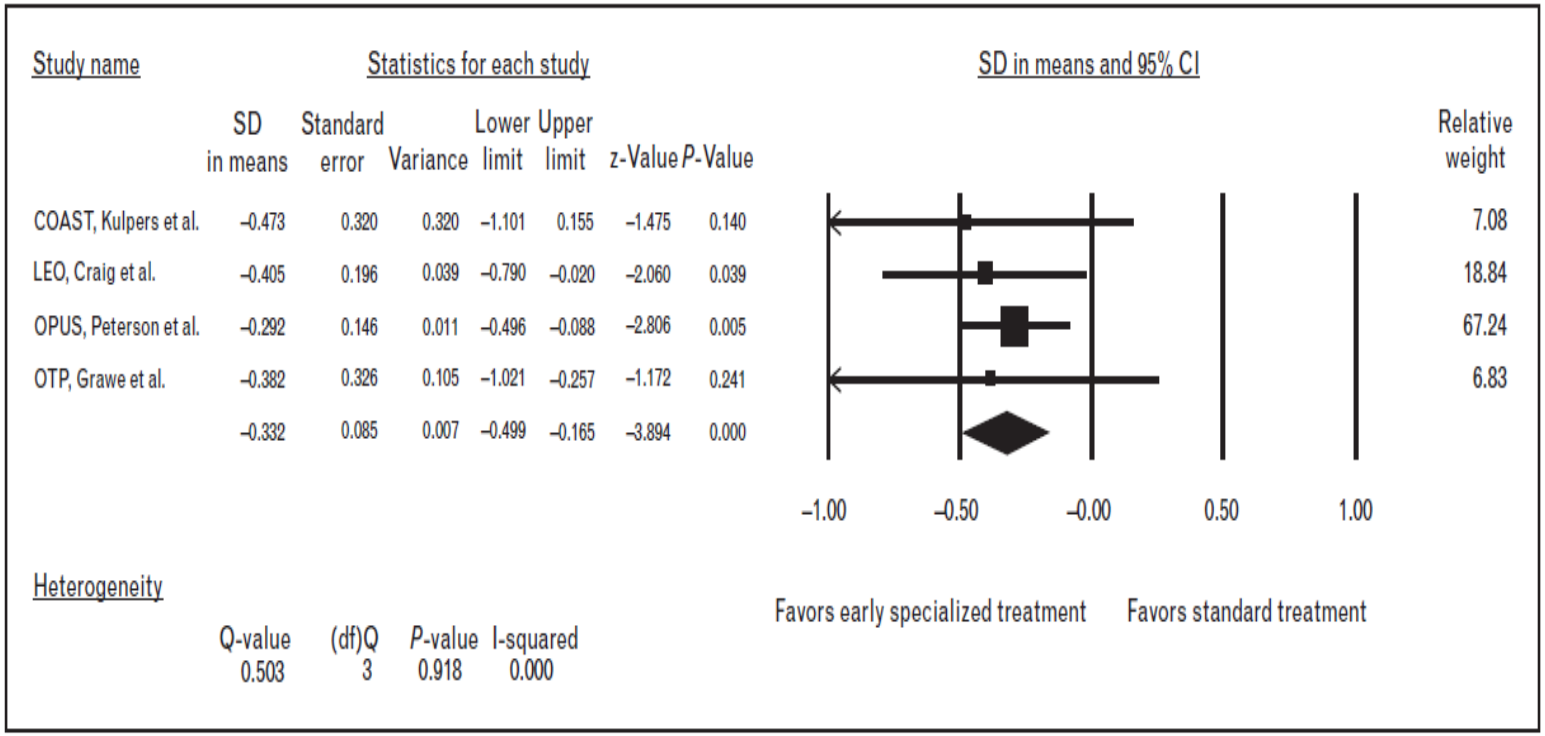

FIGURE 1. Forest plot proportion admitted. CI, confidence interval.

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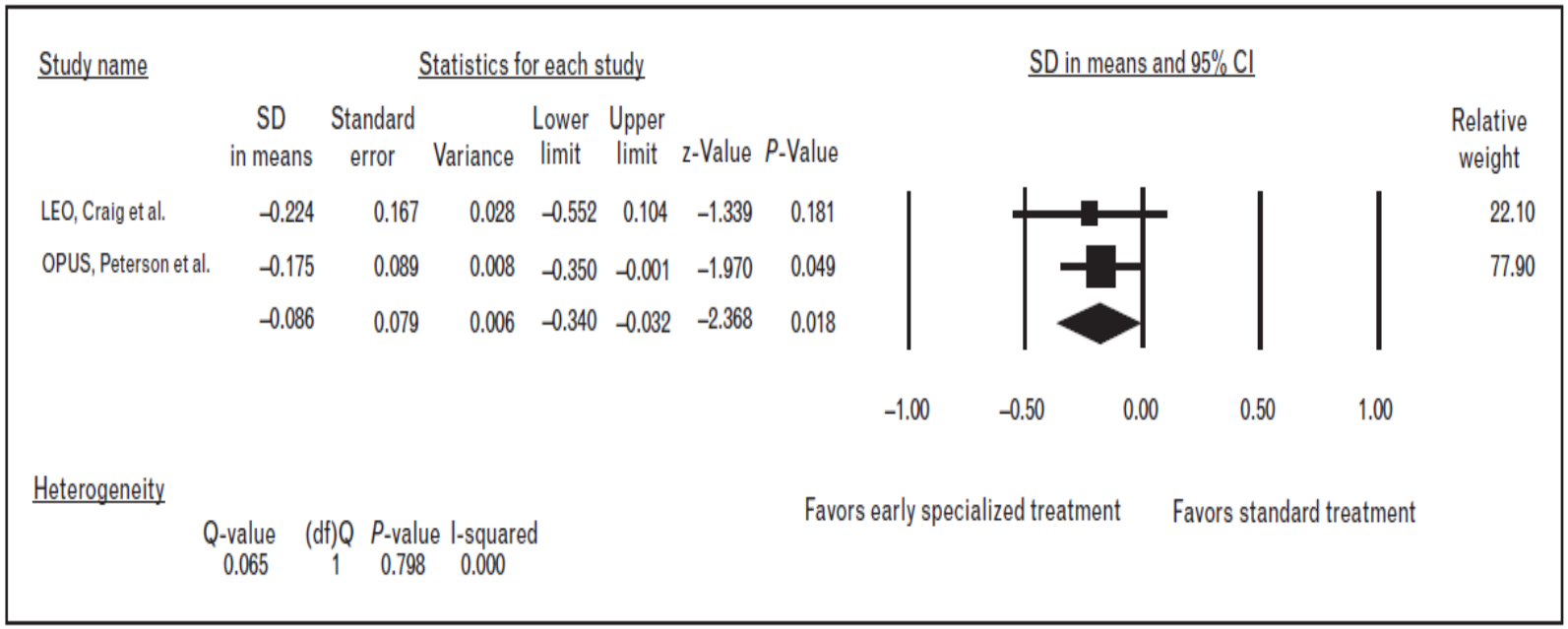

FIGURE 2. Forest plot, bed days. CI, confidence interval.

Curr Opin Psychiatry 2014, 27:167–172

Schizophrenia Bulletin vol. 41 no. 5 pp. 1192–1203, 2015
doi:10.1093/schbul/sbv058
Advance Access publication May 20, 2015

Feasibility and Effectiveness of a Multi-Element Psychosocial Intervention for First-Episode Psychosis: Results From the Cluster-Randomized Controlled GET UP PIANO Trial in a Catchment Area of 10 Million Inhabitants

Mirella Ruggeri*[,1,2], Chiara Bonetto[1], Antonio Lasalvia[1,2], Angelo Fioritti[3], Giovanni de Girolamo[4], Paolo Santonastaso[5], Francesca Pileggi[3], Giovanni Neri[6,7], Daniela Ghigi[8], Franco Giubilini[9], Maurizio Miceli[10], Silvio Scarone[11], Angelo Cocchi[12], Stefano Torresani[13], Carlo Faravelli[14], Carla Cremonese[15], Paolo Scocco[16], Emanuela Leuci[9], Fausto Mazzi[17], Michela Pratelli[8], Francesca Bellini[8], Sarah Tosato[1,2], Katia De Santi[1,2], Sarah Bissoli[1], Sara Poli[1], Elisa Ira[1], Silvia Zoppei[1], Paola Rucci[3,7], Laura Bislenghi[12], Giovanni Patelli[12], Doriana Cristofalo[1], Anna Meneghelli[12], and The GET UP Group[18]

Table 4. Primary and Secondary Outcomes: PANSS, PSYRATS, GAF, and HAMILTON of Intention to Treat Patients Assessed at Baseline (BL) (After Clinical Stabilization) and at 9-Month Follow-Up (FU). Total Number of Days of Hospitalization During the Period Between Baseline (After Clinical Stabilization) and 9-Month Follow-Up, Together With Weighted Regression Coefficients of Experimental Treatment vs Treatment as Usual (95% CI) and Effect Sizes (95% CI)

	Treatment as Usual Group		Experimental Treatment Group				
Primary Outcomes	BL (n = 172)	FU (n = 153)	BL (n = 272)	FU (n = 239)	Weighted Regression Coefficient[#] of Experimental Treatment vs Treatment as Usual (95% CI)	P-Value	Effect Size[°] (95% CI)
PANSS total	2.32 (0.68)	1.78 (0.64)	(1 missing) 2.37 (0.67)	(1 missing) 1.67 (0.57)	−0.11 (−0.22 to −0.01)	.044	−0.24 (−0.47 to −0.01)
PANSS positive	2.22 (0.86)	1.52 (0.70)	(2 missing) 2.30 (0.88)	(2 missing) 1.46 (0.57)	−0.07 (−0.18 to 0.04)	.232	−0.15 (−0.36 to 0.07)
PANSS negative	2.56 (1.11)	(4 missing) 2.01 (0.99)	(3 missing) 2.51 (1.14)	(2 missing) 1.87 (0.94)	−0.12 (−0.29 to 0.04)	.149	−0.17 (−0.37 to 0.03)
PANSS general	2.27 (0.67)	1.81 (0.64)	(1 missing) 2.35 (0.65)	(3 missing) 1.68 (0.56)	−0.14 (−0.25 to −0.03)	.015	−0.29 (−0.52 to −0.06)
Hospital admissions Total number of days of hospitalization mean (SD) [median; range]	Period between BL and FU (n = 163) 5.4 (20.2) [0; 0−150]		Period between BL and FU (n = 264) 4.6 (15.2) [0; 0−150][§]		−0.88 (−4.05, 2.29)	.586	−0.08 (−0.33 to 0.18)

	Treatment as Usual Group		Experimental Treatment Group				
Secondary Outcomes	BL (n = 172)	FU (n = 153)	BL (n = 272)	FU (n = 239)	Weighted Regression Coefficient[#] of Experimental Treatment vs Treatment as Usual (95% CI)	P-Value	Effect Size[°] (95% CI)
GAF score	(1 missing) 45.69 (12.96)	(1 missing) 60.11 (16.63)	(1 missing) 44.46 (13.81)	63.15 (16.94)	3.98 (1.15 to 6.82)	.006	0.35 (0.06 to 0.64)
HAMILTON score	(2 missing) 16.42 (9.90)	(5 missing) 10.62 (10.17)	(1 missing) 17.29 (8.29)	(3 missing) 8.81 (6.58)	−1.86 (−3.40 to −0.31)	.019	−0.25 (−0.48 to −0.03)
PSYRAT auditory hallucination scale	N = 22[a] 2.03 (1.25)	N = 22 0.51 (1.08)	N = 29[b] 1.67 (1.34)	N = 29 0.41 (0.93)	−0.17 (−0.75 to 0.42)^	.580	−0.23 (−1.13 to 0.66)
PSY AHS distress	2.13 (1.52)	0.76 (1.48)	1.69 (1.57)	0.48 (1.09)	−0.40 (−1.21 to 0.40)^	.328	−0.62 (−1.85 to 0.62)
PSY AHS cognitive	2.38 (1.39)	0.57 (1.08)	1.94 (1.48)	0.42 (0.90)	−0.25 (−0.90 to 0.39)^	.443	−0.35 (−1.29 to 0.60)
PSY AHS physical	1.87 (1.19)	0.45 (0.97)	1.56 (1.27)	0.40 (0.94)	−0.09 (−0.61 to 0.45)^	.772	−0.07 (−0.82 to 0.68)
PSYRAT delusion scale	N = 31[c] 2.78 (1.15)	N = 31 1.59 (1.38)	N = 50[d] 3.12 (0.73)	N = 50 0.76 (1.11)	−0.96 (−1.52 to −0.39)^	.001	−0.82 (−1.29 to −0.35)
PSY DS distress	2.62 (1.38)	1.60 (1.53)	3.05 (0.97)	0.75 (1.12)	−0.93 (−1.59 to −0.28)^	.005	−0.78 (−1.32 to −0.23)
PSY DS cognitive	2.84 (1.14)	1.65 (1.45)	3.15 (0.77)	0.77 (1.12)	−1.01 (−1.56 to −0.46)^	.000	−0.86 (−1.32 to −0.39)

Very Early Intervention: does it works?

"The evidence available up to the time of the literature search does not allow for recommendation of early intervention targeting prodromal or at-risk patients *to prevent progression from the prodromal phase to acute, full-blown psychosis, nor to improve prognosis.* ***Conversely, identification and timely treatment of first-episode psychotic patients through specific early intervention programmes are highly recommended****.*

De Masi S et al, The Italian Guidelines for early intervention in schizophrenia Developments and conclusions, Wearly Interv Psychiatry,2008,2:291:302

Early Intervention: does it works?

*"**There is emerging, but as yet inconclusive evidence, to suggest that people in the prodrome of psychosis can be helped by some interventions**. There is **some support for specialised early intervention services**, but further trials would be desirable, and there is a question of whether gains are maintained. There is some support for phase-specific treatment focused on employment and family therapy, but again, this needs replicating with larger and longer trials"*

Marshall M, Rathbone J, Early Intervention for Psychosis, Cochrane Database Syst Rev,2011,Jun 15,(6):CD004718

- Recovery; definizioni, modell di intervento

Il recovery come processo individuale di ricostruzione di senso dell'esistenza

"processo unico, profondamente personale di cambiamento dei propri atteggiamenti, valori, sentimenti, obiettivi, abilità e/o ruoli. ***Rappresenta una modalità di vivere una vita soddisfacente, carica di speranza e ricca di spunti pur con le limitazioni causate dalla malattia.*** *La ripresa coinvolge lo sviluppo di nuovi significati e scopi della propria vita, al di là degli effetti catastrofici della malattia mentale".*

Anthony,1993

'Recovery is what people experience themselves as they become ***empowered to manage their lives*** *in a manner that allows them to* ***achieve a fulfilling, meaningful life*** *and a* ***contributing positive sense of belonging in their communities***'

National Institute for Mental Health in England,2005.

Recovery from schizophrenia and the recovery model

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Current Opinion in Psychiatry 2009, 22:374–380

Purpose of review

The recovery model refers to subjective experiences of optimism, empowerment and interpersonal support, and to a focus on collaborative treatment approaches, finding productive roles for user/consumers, peer support and reducing stigma. The model is influencing service development around the world. This review will assess whether optimism about outcome from serious mental illness and other tenets of the recovery model are borne out by recent research.

Recent findings

Remission of symptoms has been precisely defined, but the definition of 'recovery' is a more diffuse concept that includes such factors as being productive and functioning independently. Recent research and a large, earlier body of data suggest that optimism about outcome from schizophrenia is justified. A substantial proportion of people with the illness will recover completely and many more will regain good social functioning. Outcome is better for people in the developing world. Mortality for people with schizophrenia is increasing but is lower in the developing world. Working appears to help people recover from schizophrenia, and recent advances in vocational rehabilitation have been shown to be effective in countries with differing economies and labor markets. A growing body of research supports the concept that empowerment is an important component of the recovery process.

Summary

Key tenets of the recovery model – optimism about recovery from schizophrenia, the importance of access to employment and the value of empowerment of user/consumers in the recovery process – are supported by the scientific research. Attempts to reduce the internalized stigma of mental illness should enhance the recovery process.

Keywords

employment, empowerment, outcome, recovery, schizophrenia

Curr Opin Psychiatry 22:374–380

0951-7367

Il recovery dal punto di vista clinico: remissione clinica , remissione funzionale, benessere soggettivo

“Recovery is a more demanding and longer-term phenomenon than remission”

Andreasen et al. Am J Psychiatry 2005;162:441-449

“ *There are multiple elements of recovery. These include freedom from troubling psychotic symptoms and relapses, satisfaction with life and daily activities and suitable functioning in everyday life”*

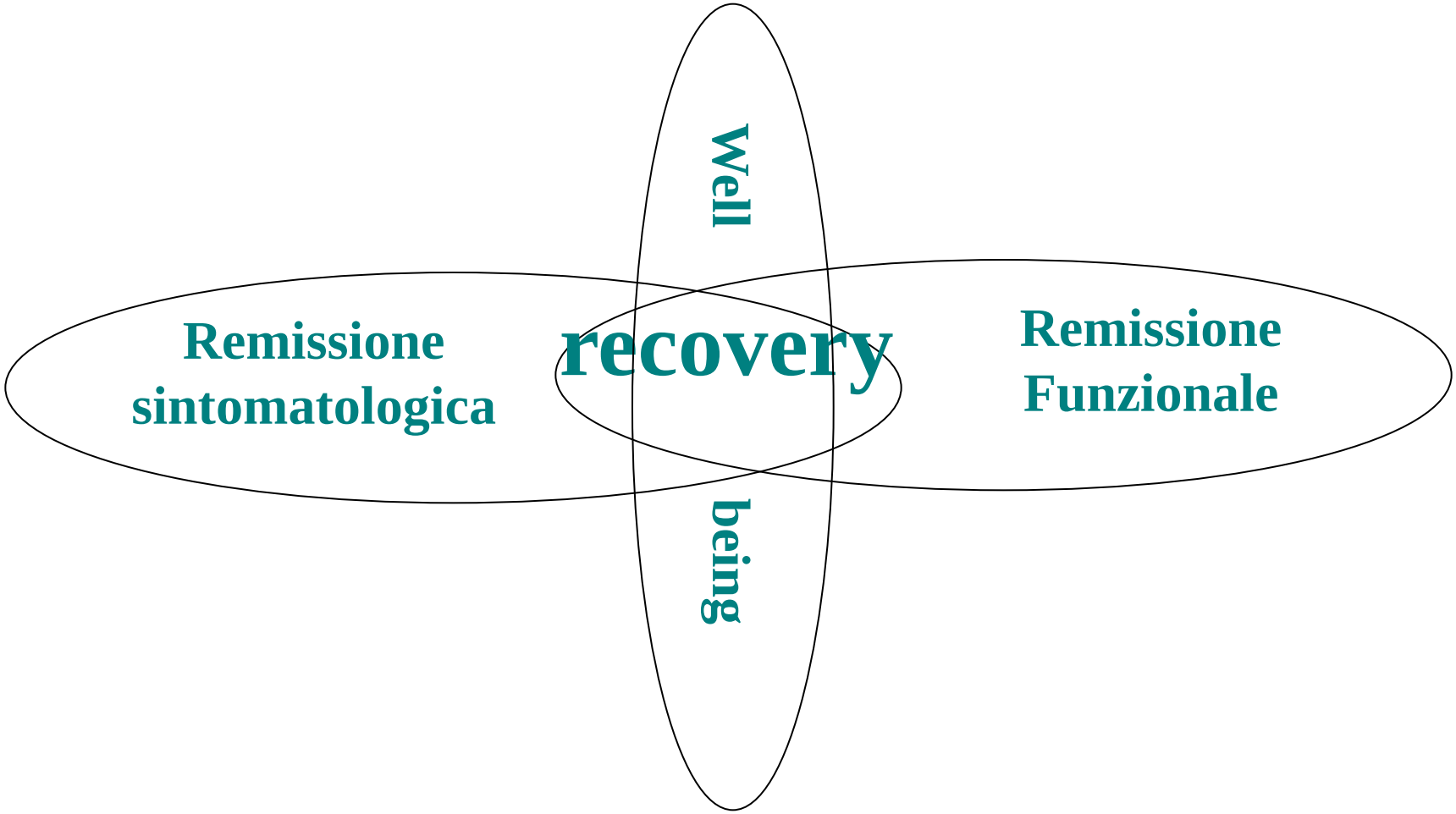
Harvey P.D,Bellack AS,Toward a terminology for functional Recovery in Schizophrenia: Is Functional Remission a Viable Concept? Schiz Bull,35,300-6, 2009

“Recovery encompasses both symptom remission and functiontal elements such as cognition, social functioning and quality of life”

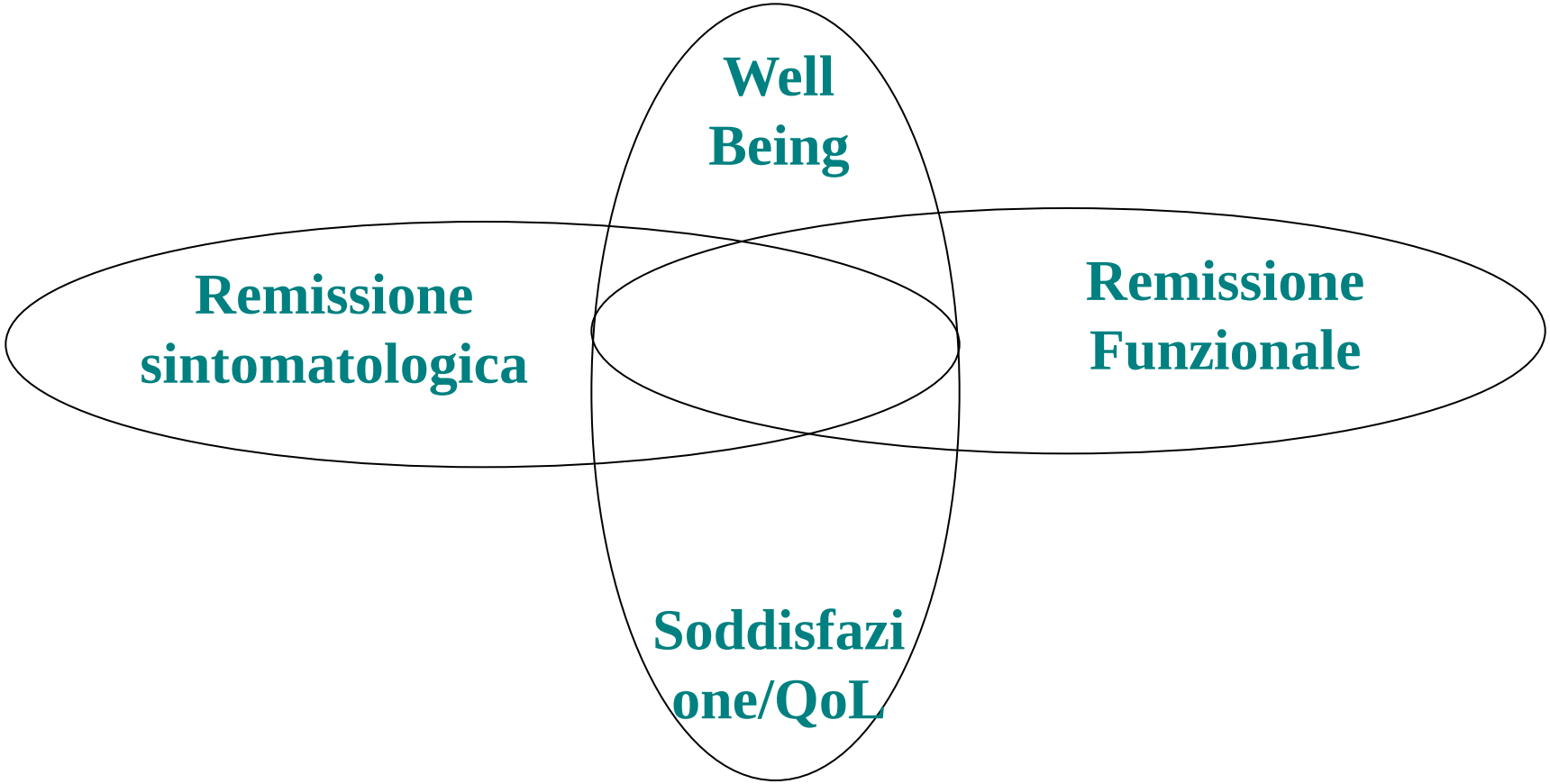
Luecht S,Lasser R,The concept of remission and recovery In Schizophrenia,Pharmacopsychiatry,39:161-70,2005

Modelli clinici del recovery.1

Modelli clinici del recovery.2



Modelli clinici del recovery.3



Recovery dal punto di vista clinico : un termine in cerca di criteri condivisi

Criteri di Recovery

variabile	studio		
	Harding et al,1987	**Liberman et al,2002**	**Torgalsboen et al,2002**
Sintomatologia	*Assenza di sintomi;no farmaci*	*Punteggio BPRS =/<4 a tutti i sintomi positivi e negativi*	*Nessun ricovero in 5 anni*
Funziona mento	*Vita sociale sovrapponibile a quella dei vicini; presenza di un lavoro retribuito o volontario*	*Lavoro almeno a tempo parziale o ins.scolastico;gestione autonoma danaro e farmaci; attività sociali almeno 1 volta alla settimama*	*Punteggio GAF superiore a 65*
Benessere soggettivo/Qol	*Non considerato*	*Non considerato*	*Non considerato*
Durata	*Non indicata*	*Due anni*	*Cinque anni*

Criteri di Recovery

variabile	studio		
	Whitehorn et al,2001	**Lambert et al 2006**	**Harrow & Job,2007**
Sintomatologia	*Punteggio PANSS =/<4 a tutte le scale*	*Punteggio =/<3 alle dimensioni positiva,negativa,de pressiva e cognitiva della CGI-Schiz.*	*Assenza di sintomi psicotici*
Funziona mento	*GAF >50*	*Lavoro almeno part-time* *Autonomia nella vita quotidiana (vive da solo o con amici o partner)*	*Adeguato adattamento* *Lavorativo ed accettabile funzionamento sociale*
Benessere soggettivo/Qol	*Non considerato*	*Punteggio =/>80 alla SWN-K*	*Non considerato*
Durata	*Due anni*	*Sei mesi*	*Un anno*

- *Remission of symptoms*
- *Engagement in productive activity (Work,school)*
- *Independent management of day-to-day needs*
- *Cordial family relations*
- *Recreational activities*
- *Satisfying peer relationships*

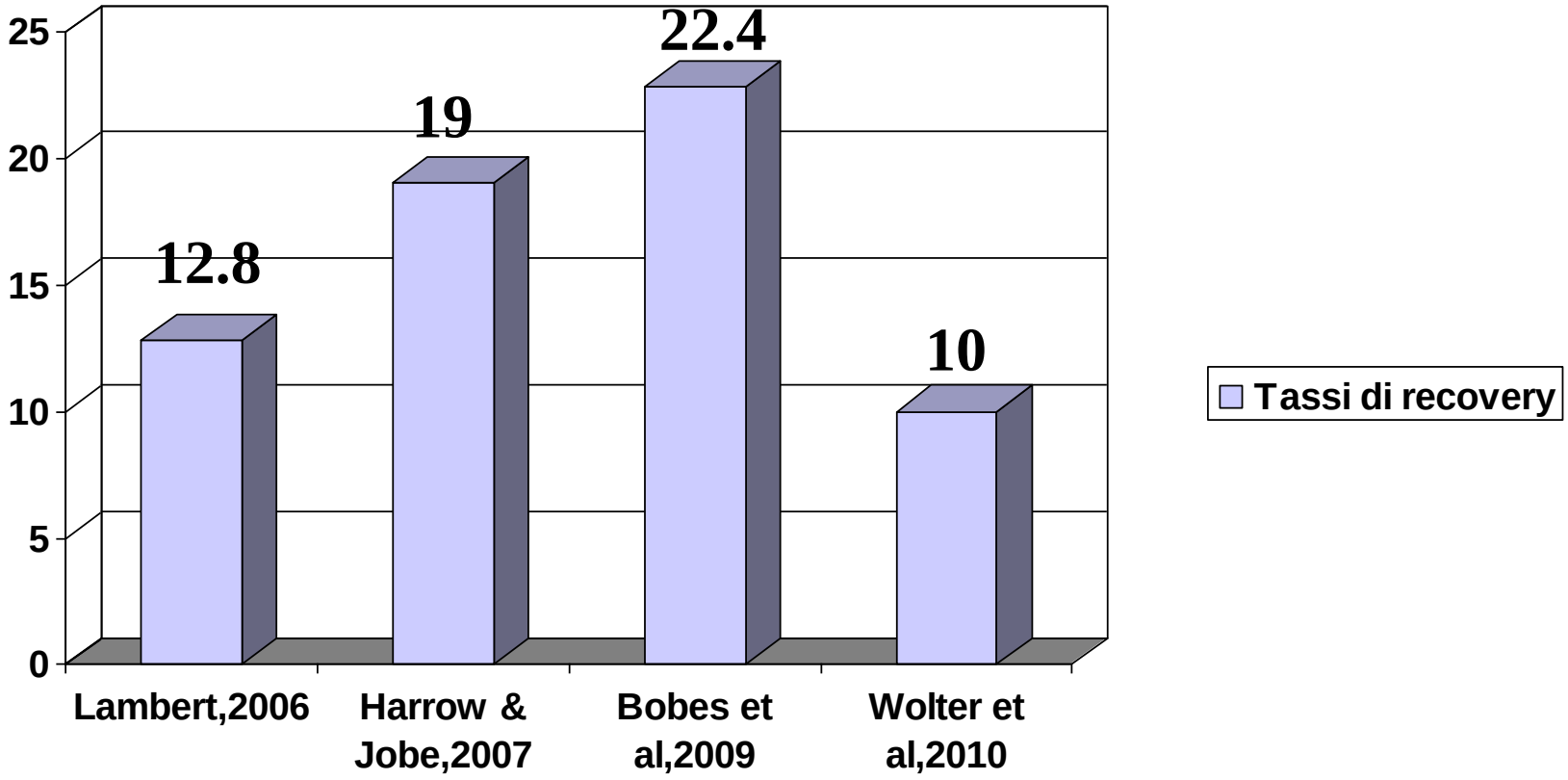
Liberman RP,Recovery from disability.Manual of psychiatric Rehabilitation,Am Psych Publishing,Washington DC,2008

Recovery is possible

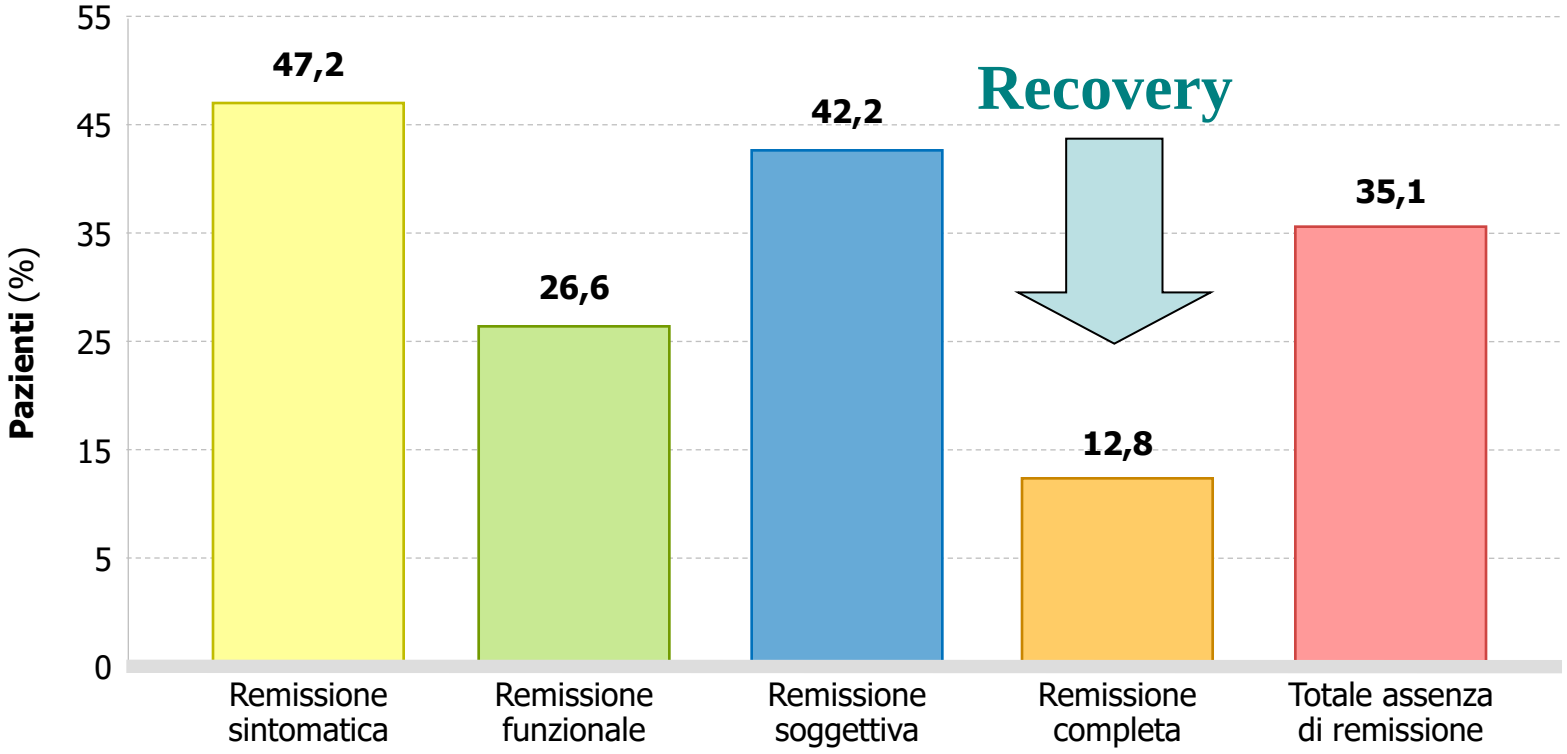
“ *Now is accepted that **recovery is possible**, even to the extent of full absence of all symptoms and disabilities and that optimal recovery should be a goal for people with schizophrenia,although not all the individual with the illness will make significant progress toward this goal”*

Harvey P.D,Bellack AS,Toward a terminology for functional Recovery in Schizophrenia: Is Functional Remission a Viable Concept? Schiz Bull,35,300-6, 2009

Tassi di recovery



Tassi di remissione a 24 mesi di follow-up **(studio SOHO)**



Lambert et al. J Clin Psychiatry 2006;67:1690-1697

Remissione sintomatologica,funzionale,soggettiva 24 mesi in 2960 pazienti

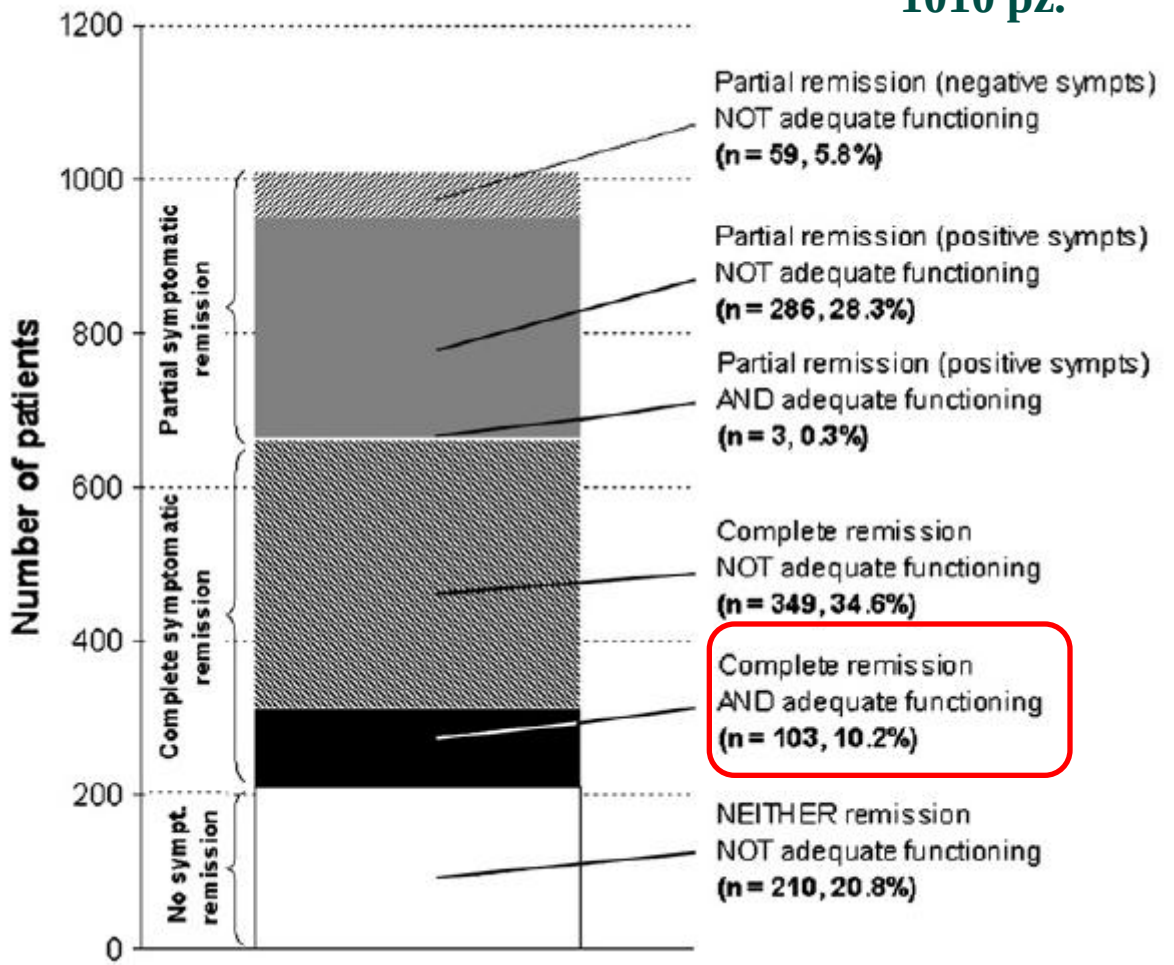
Remissione sintomatologica	Remissione funzionale	Benessere soggettivo	%
NO	***NO***	***NO***	***35,08***
SI	*NO*	*NO*	*11,12*
NO	*SI*	*NO*	*7,19*
NO	*NO*	*SI*	*8,30*
SI	*SI*	*NO*	*4,37*
SI	*NO*	*SI*	*18.86*
NO	*SI*	*SI*	*2.24*
SI	***SI***	***SI***	***12.84***

Lambert et al. J Clin Psychiatry 2006;67:1690-1697

Symptomatic remission and social/vocational functioning in outpatients with schizophrenia: Prevalence and associations in a cross-sectional study

Luis San [a], Antonio Ciudad [b,*], Enrique Álvarez [c], Julio Bobes [d], Inmaculada Gilaberte [b]

1010 pz.



Cagliari Recovery Study

Gender Differences in Remission and Recovery of Schizophrenic and Schizoaffective Patients: Preliminary Results of a Prospective Cohort Study
Schizophrenia Research and Treatment
Volume 2012, . doi:10.1155/2012/576369

Criteria for symptom remission revisited: a study of patients affected by schizophrenia and schizoaffective disorders
BMC Psychiatry 2013, **13**:235

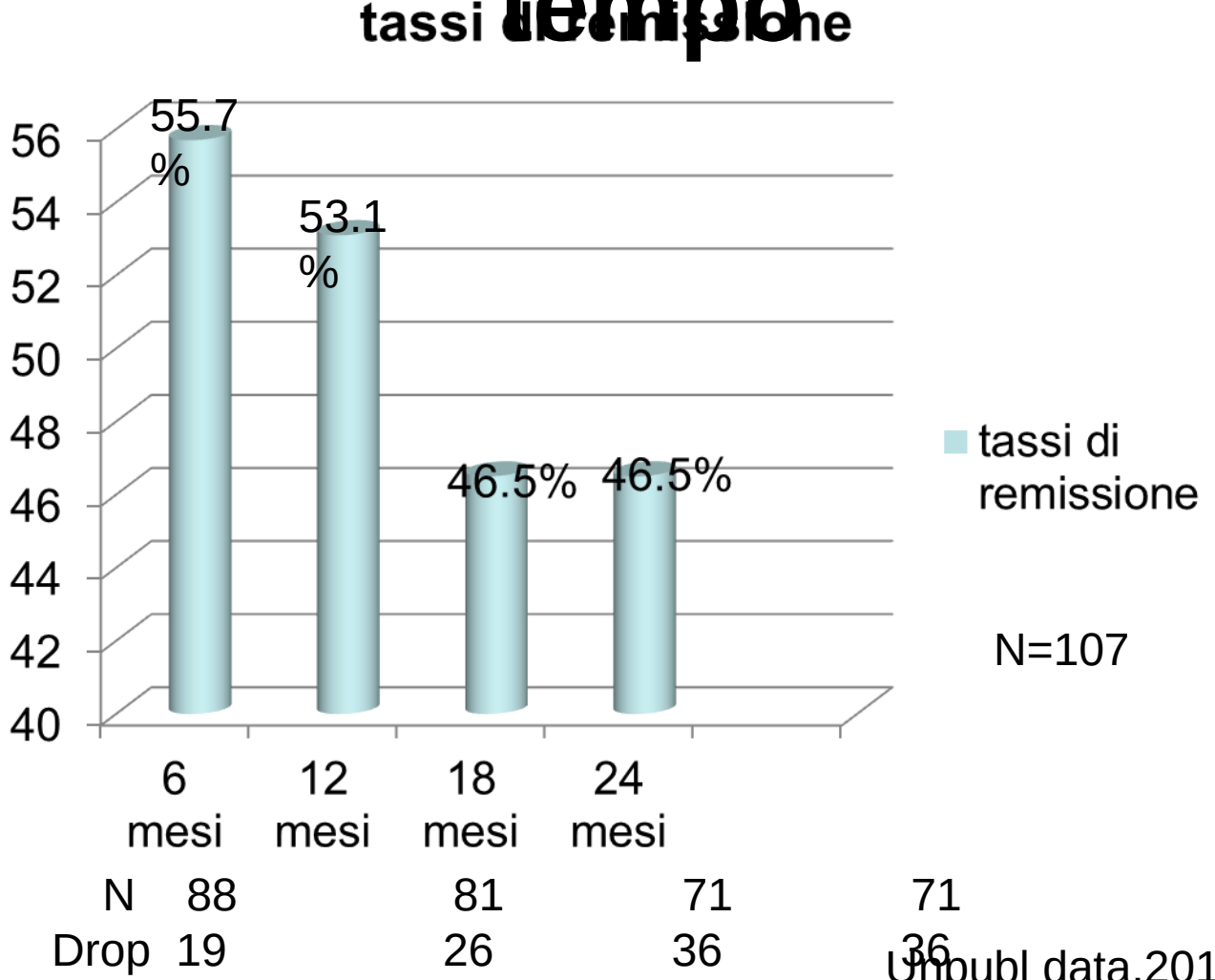
Is it true remission? A study of remitted patients affected by schizophrenia and schizoaffective disorders
Psychiatry Research 210 (2013) 739–744

Long-term outcome of schizoaffective disorder.
Are there any differences with respect to schizophrenia?
Riv Psichiatr 2014; 49(1): 41-49

Consensus five factor PANSS for evaluation of clinical remission: effects on functioning and cognitive performances
Schizophrenia Research: Cognition 1 (2014) 187–192

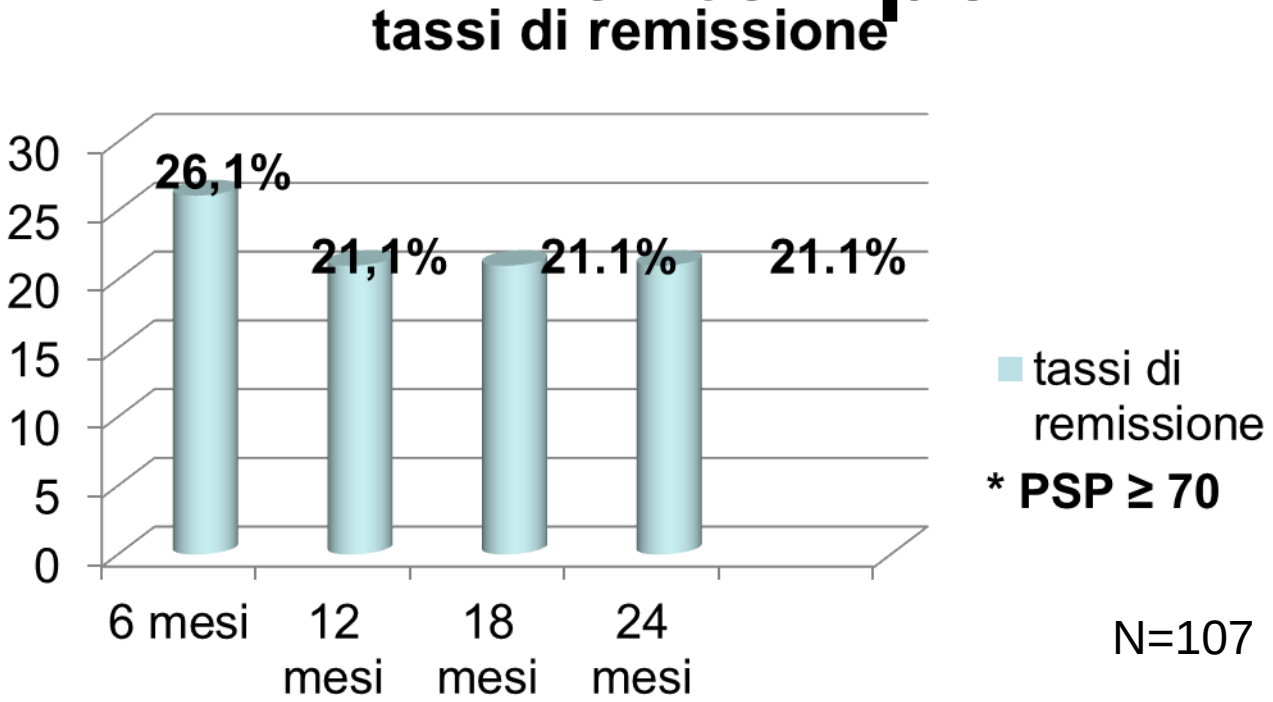
Clinical Global Impression-severity score as a reliable measure for routine evaluation of remission in schizophrenia and schizoaffective disorders
Annals of General Psychiatry (2015) 14:6

Cagliari Recovery Study: tenuta della remissione clinica nel tempo



Unpubl data,2015

Cagliari Recovery Study: tenuta della remissione funzionale* nel tempo



N=107

N	88		81	
71		71		
Drop	19		26	

Unpubl data,2015

Cagliari Recovery Study
Tassi di recovery

Criteri di recovery	Schizofrenia	Schizoaffettivo	Totali
Rem clinica+ remiss funzionale	4,8%*	17,2%*	**12.0%**
Rem clinica+ benessere sogg	26,2%	33,3%	**30.3%**
Rem Clin+ rem funzion+ Beness sogg	2,4%	10,3%	**7%**

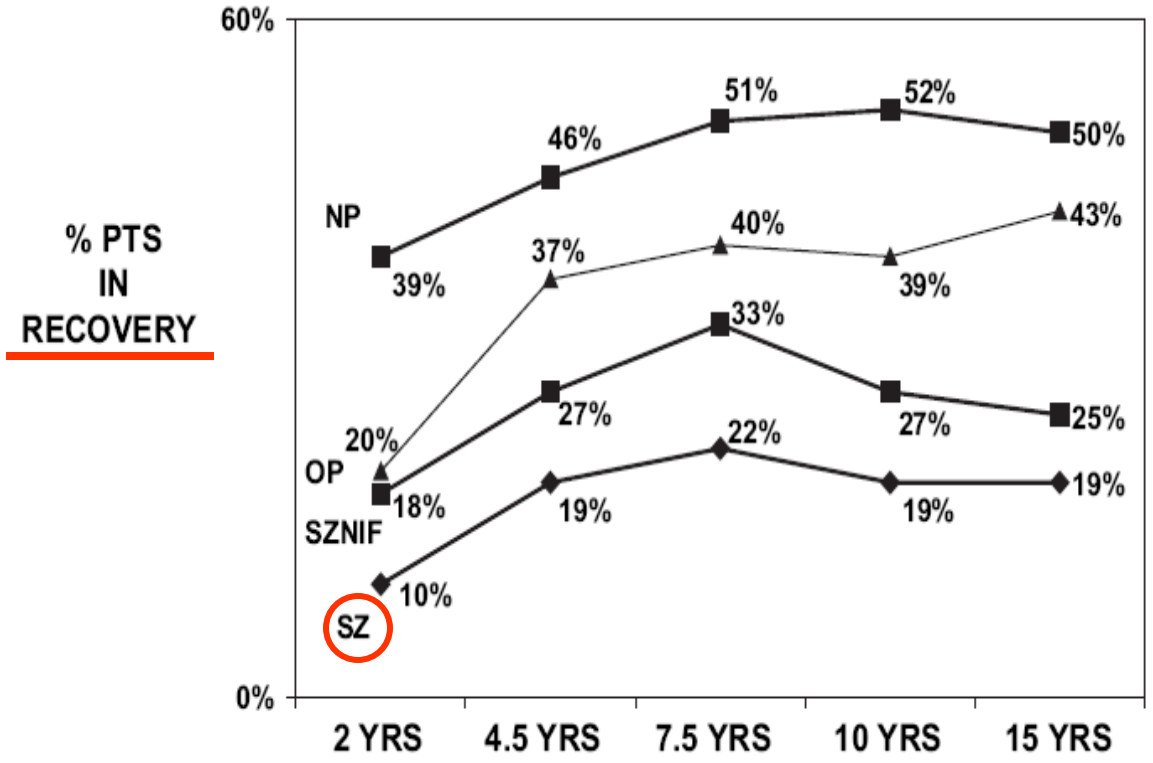
Carpiniello et al, Schizoph Res Treatm, 2012

* p=0.053

Do Patients with Schizophrenia Ever Show Periods of Recovery? A 15-Year Multi-Follow-up Study

Schizophrenia Bulletin vol. 31 no. 3 pp. 723–734, 2005

many views of recovery include the absence of major symptoms and adequate instrumental work functioning and psychosocial functioning.



Schizophrenia Bulletin vol. 39 no. 6 pp. 1296–1306, 2013
doi:10.1093/schbul/sbs130
Advance Access publication November 20, 2012

A Systematic Review and Meta-Analysis of Recovery in Schizophrenia

Erika Jääskeläinen[*,1,6], Pauliina Juola[1], Noora Hirvonen[1,2], John J. McGrath[3,4], Sukanta Saha[3], Matti Isohanni[1], Juha Veijola[1], and Jouko Miettunen[1,5,6]

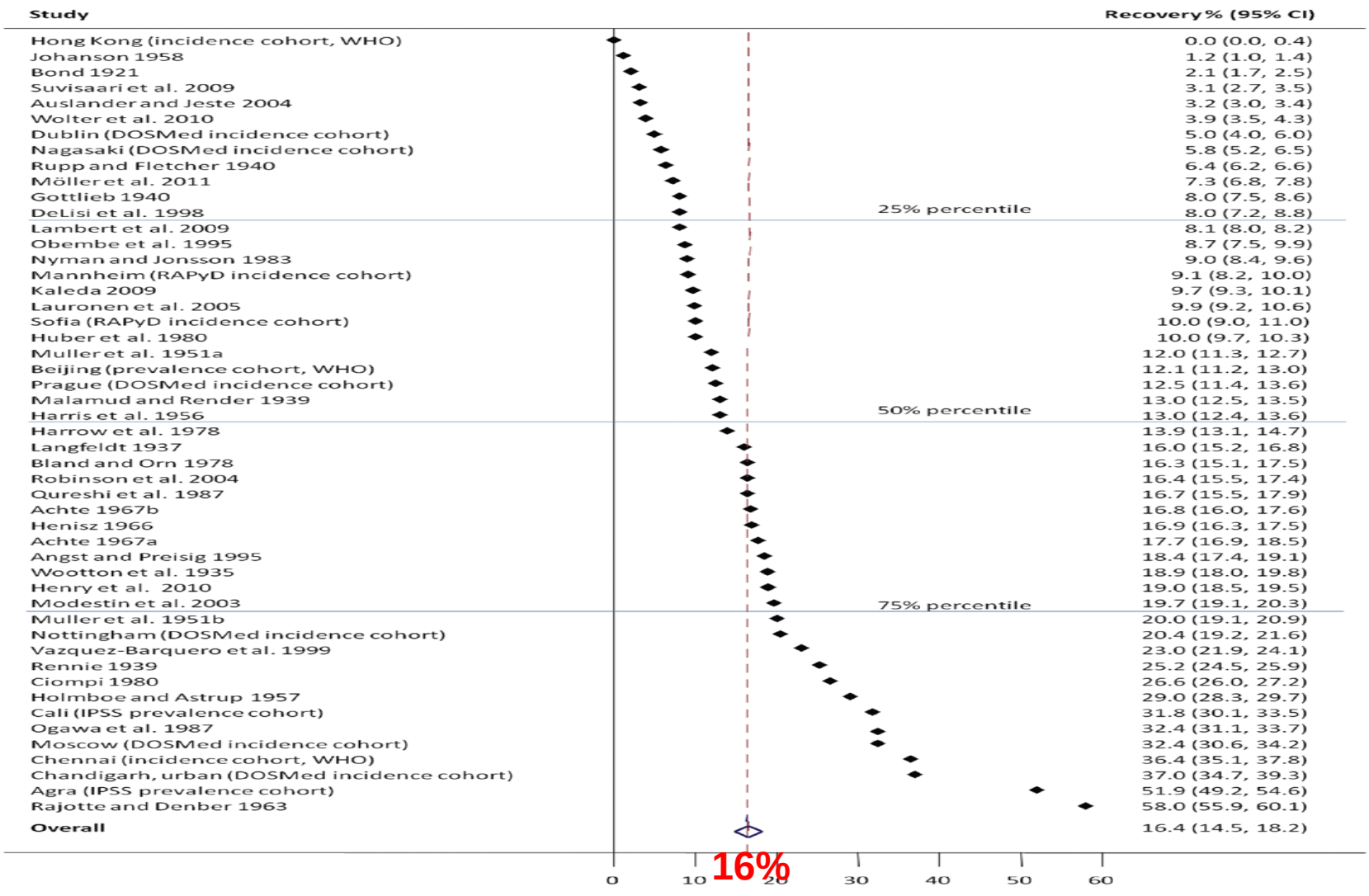


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Table 1. Recovery Percentages in Subpopulations

	Number of Studies	Median%[a]	IQR[b]	Statistical Test[c]
Sex	24			$t = 1.08$, $P = .293$
Males	12	12.9	10.0–19.4	—
Females	12	12.1	7.5–29.0	—
Midpoint of the collection of the sample[d]	48			$t = -0.38$, $P = .704$
Before 1941	11	13.0	6.4–20.0	—
1941–1955	5	17.7	13.0–19.7	—
1956–1975	11	16.9	16.3–32.4	—
1976–1995	19	9.9	5.8–19.0	—
After 1996	2	6.0	3.9–8.1	—
Economic index of the site[e]	50			$t = -2.93$, $\mathbf{P = .005}$
Low or lower-middle	5	36.4	16.7–37.0	—
Upper-middle	5	12.1	10.0–31.8	—
High	40	13.0	7.7–19.0	—
First-episode vs not first-episode samples	46			$t = -0.18$, $P = .857$
First-episode sample	30	16.6	9.0–20.4	—
Not first-episode sample	16	11.1	6.0–22.5	—
Origin of the sample	46			$t = 0.25$, $P = .802$
Discharge cohort	6	15.3	13.0–32.4	—
Admission cohort	24	14.5	8.4–18.7	—
Cohort including out- and inpatients or general population	16	12.3	7.5–26.1	—
Length of follow-up	50			$t = 0.91$, $P = .369$
2–5 y	13	13.9	8.1–17.7	—
>5–10 y	9	10.0	8.0–16.0	—
>10–15 y	15	16.3	9.1–29.0	—
>15 y	13	18.4	9.7–26.6	—
Diagnostic criteria[f]	33			$t = 0.86$, $P = .396$
Kraepelinian	12	9.0	4.8–17.3	—
Non-Kraepelinian	21	12.5	9.1–31.8	—
WHO study	50			$t = 1.34$, $P = .185$
Yes	13	12.5	9.1–32.4	—
No	37	13.9	8.1–18.9	—
Quality of the study	50			$t = 0.27$, $P = .792$
Quality score < median	23	16.0	9.0–18.9	—
Quality score ≥ median	27	12.5	8.0–23.0	—

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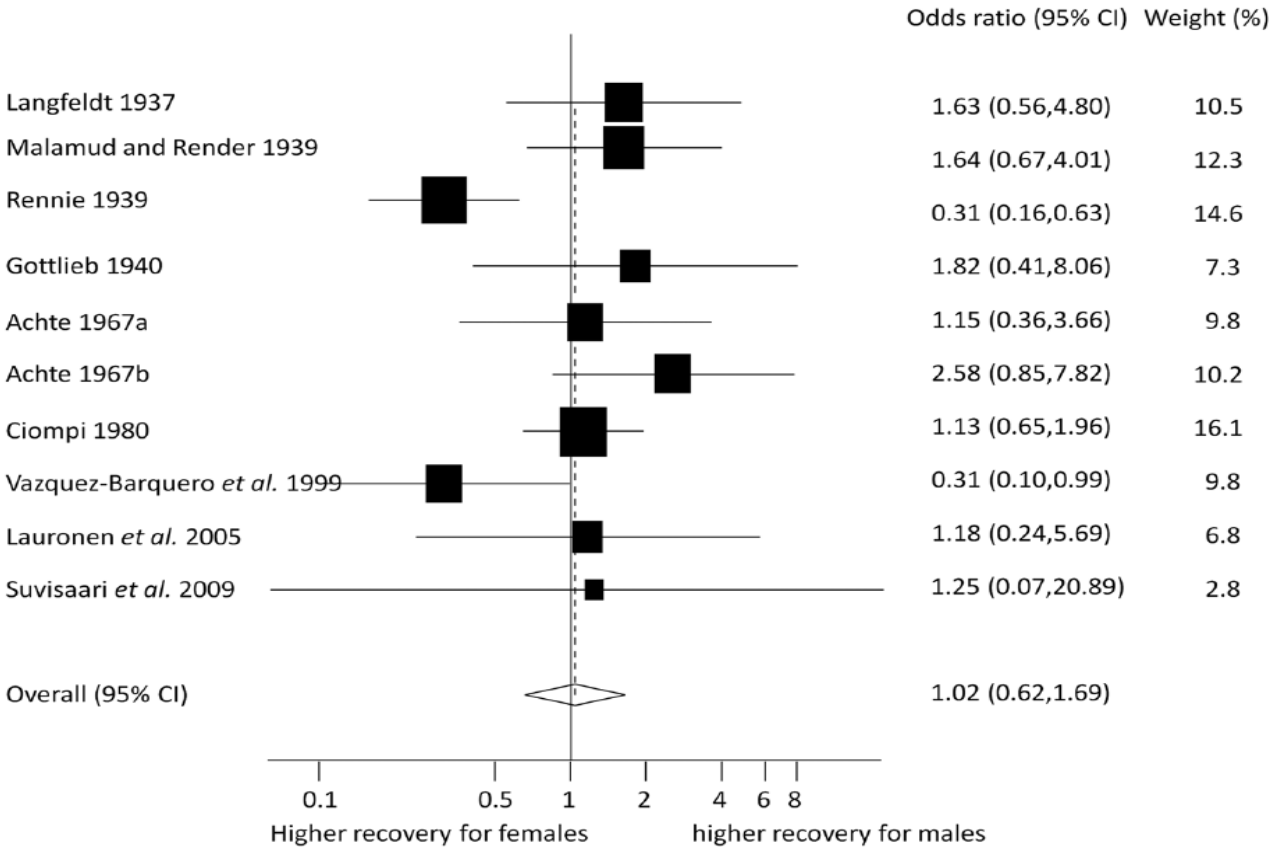


Interventi clinici e psicosociali orientati al recovery

- Intervento precoce finalizzato al raggiungimento e al mantenimento remissione (prevenzione recidive)
- Continuità dell'intervento nel tempo
- Interventi cognitivi
- Interventi psicosociali finalizzati al mantenimento o recupero delle abilità personali e sociali e all'inserimento/reinserimento lavorativo e sociale
- Interventi finalizzati all'empowerment
- Interventi sulla famiglia
- Lotta allo stigma

- Interventi orientati al recovery: ruolo dell’intervento farmacologico

Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis

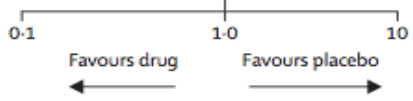
Stefan Leucht, Magdalena Tardy, Katja Komossa, Stephan Heres, Werner Kissling, Georgia Salanti, John M Davis

Summary

Background Relapse prevention with antipsychotic drugs compared with placebo in patients with schizophrenia has not been sufficiently addressed by previous systematic reviews. We aimed to assess the association between such drugs and various outcomes in patients with schizophrenia to resolve controversial issues.

Published Online May 3, 2012
DOI:10.1016/S0140-6736(12)60239-6

	Number of studies included	Drug group	Control group	Mean study duration* (months)	Risk ratio (95% CI)	Absolute difference (95% CI)	NNTB/H (95% CI)
Relapse 7–12 months	24	392/1465 (27%)	773/1204 (64%)	11	0·40 (0·33 to 0·49)	−0·39 (−0·46 to −0·32)	3 (2 to 3)
Relapse independent of duration	62	744/3395 (22%)	1718/2997 (57%)	9	0·35 (0·29 to 0·41)	−0·38 (−0·43 to −0·33)	3 (2 to 3)
Participants readmitted to hospital	16	112/1132 (10%)	245/958 (26%)	13	0·38 (0·27 to 0·55)	−0·19 (−0·27 to −0·11)	5 (4 to 9)
Dropout for any reason	57	802/2642 (30%)	1130/2076 (54%)	9	0·53 (0·46 to 0·61)	−0·24 (−0·30 to −0·17)	4 (3 to 6)
Dropout because of inefficacy	46	412/2539 (16%)	830/2007 (41%)	8	0·37 (0·31 to 0·44)	−0·27 (−0·34 to −0·19)	4 (3 to 5)
Participants unimproved/worse	14	614/880 (70%)	569/644 (88%)	5	0·73 (0·64 to 0·84)	−0·25 (0·35 to 0·14)	4 (3 to 7)
Violent/aggressive behaviour	5	9/403 (2%)	34/277 (12%)	8	0·27 (0·15 to 0·52)	−0·09 (−0·17 to −0·01)	11 (6 to 100)
Participants employed	2	63/130 (48%)	65/129 (50%)	11	0·96 (0·75 to 1·23)	−0·02 (−0·14 to 0·10)	50 (H7 to B10)†
Death (any)	14	5/1240 (<1%)	7/1116 (1%)	7	0·77 (0·28 to 2·11)	0·00 (−0·01 to 0·00)	∞
Suicide	8	0/1021	2/920 (<1%)	6	0·34 (0·04 to 3·28)	0·00 (−0·01 to 0·00)	∞
Death from natural causes	14	5/1272 (1%)	3/1129 (<1%)	7	1·24 (0·39 to 3·97)	0·00 (0·00 to 0·01)	∞
Dropout because of AE	43	129/2437 (5%)	78/1896 (4%)	8	1·16 (0·70 to 1·91)	0·00 (−0·01 to 0·02)	∞
At least one AE	10	575/1188 (48%)	450/996 (45%)	7	1·01 (0·87 to 1·18)	0·01 (−0·06 to 0·08)	100 (H17 to B13)†
At least one MD	22	304/1901 (16%)	134/1510 (9%)	7	1·55 (1·25 to 1·93)	0·06 (0·03 to 0·10)	17 (10 to 33)
Dyskinesia	13	18/1051 (2%)	37/769 (5%)	9	0·52 (0·28 to 0·97)	−0·01 (−0·02 to 0·01)	100 (H50 to B100)†
Use of antiparkinsonian medication	7	182/748 (24%)	90/569 (16%)	7	1·40 (1·03 to 1·89)	0·09 (0·02 to 0·16)	11 (6 to 50)
Sedation	10	158/1174 (13%)	85/972 (9%)	6	1·50 (1·22 to 1·84)	0·05 (0·00 to 0·10)	20 (B=∞ to H10)†
Weight gain	10	128/1231 (10%)	61/1090 (6%)	7	2·07 (2·31 to 3·25)	0·05 (0·03 to 0·07)	20 (14 to 33)



Lancet 2012; 379:2063-71

Patient Preference and Adherence

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REVIEW

Impact of long-acting injectable antipsychotics on medication adherence and clinical, functional, and economic outcomes of schizophrenia

Gabriel Kaplan[1,2]
Julio Casoy[3]
Jacqueline Zummo[3]

This article was published in the following Dove Press journal:
Patient Preference and Adherence

Abstract: Schizophrenia is a debilitating chronic disease that requires lifelong medical care and supervision. Even with treatment, the majority of patients relapse within 5 years, and suicide may occur in up to 10% of patients. Poor adherence to oral antipsychotics is the most common cause of relapse. The discontinuation rate for oral antipsychotics in schizophrenia ranges from 26% to 44%, and as many as two-thirds of patients are at least partially non-adherent, resulting in increased risk of hospitalization. A very helpful approach to improve adherence in schizophrenia is the use of long-acting injectable (LAI) antipsychotics, although only a minority of patients receive these. Reasons for underutilization may include negative attitudes, perceptions, and beliefs of both patients and health care professionals. Research shows, however, significant improvements in adherence with LAIs compared with oral drugs, and this is accompanied by lower rates of discontinuation, relapse, and hospitalization. In addition, LAIs are associated with better functioning, quality of life, and patient satisfaction. A need exists to encourage broader LAI use, especially among patients with a history of nonadherence with oral antipsychotics. This paper reviews the impact of nonadherence with antipsychotic drug therapy overall, as well as specific outcomes of the schizophrenia patient, and highlights the potential benefits of LAIs.

Potenziali vantaggi degli antipsicotici iniettabili "Long-Acting" (LAI)

- Rapida identificazione della non aderenza totale e superamento di quella parziale
- Riduzione del rischio di sintomi e recidive da sospensione improvvisa
- Ridotta probabilità di overdose accidentale o deliberata
- Migliore biodisponibilità del principio attivo e stabilità dei parametri farmacocinetici
- Regolarità nei contatti del paziente con l'équipe terapeutica
- Stabilizzazione del paziente a lungo termine e miglioramento degli esiti clinici e funzionali

Rethinking the role of long-acting atypical antipsychotics in the community setting

Altamura, Alfredo Carloa; Aguglia, Eugenioc; Bassi, Marianob; Bogetto, Filippod; Cappellari, Lodovicoe; De Giorgi, Serafinof; Fagiolini, Andreag; Ferrannini, Luigih; Girardi, Paoloi

Abstract

Schizophrenia is a relapsing and evolving condition, which requires treatment continuity. Increasing evidence shows that antipsychotic discontinuation is associated with relapse in most patients, and that early interventions have a positive impact on long-term outcomes. Poor adherence to antipsychotics is a major factor in the treatment of schizophrenia and a relevant risk factor for relapse. Considerable effort has been made toward improving adherence, including the development of long-acting injectable (LAI) antipsychotics. LAIs have traditionally been reserved for patients with repeated nonadherence; currently, several misconceptions prevent their more widespread use. The recent introduction of LAI formulations of atypical antipsychotics and the encouraging results in terms of the reduction in relapse rates and avoidance of hospitalization warrant a reassessment of the role of LAIs in the management of schizophrenia. This paper presents the position of a panel of nine Italian schizophrenia experts on the use of novel LAI medications, with a focus on community-based services, the prevailing setting of schizophrenia treatment in Italy. **The need to change the attitude toward LAIs – no longer a treatment of last resort, but a component of multimodal strategies leading patients to remission and rehabilitation – is emphasized.** The paper also presents recommendations for LAI atypical antipsychotic use in the community setting.

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Review

Long-acting injectable antipsychotics in early psychosis: a literature review

Robin Emsley,[1] Bonginkosi Chiliza,[1] Laila Asmal,[1] Mpogisheng Mashile[1] and Paolo Fusar-Poli[2]

Conclusions: The available evidence does suggest that long-acting injectable antipsychotics can be used safely and effectively in early stages of the illness, and that they may be associated with better outcomes than with oral medications. However, this is largely supported by evidence from naturalistic cohort studies and a small number of controlled trials of risperidone long-acting injection. Evidence for olanzapine and paliperidone long-acting injectables in particular is limited.

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Review

Treatment of early episode in patients with schizophrenia: the role of long acting antipsychotics

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The use of long-acting injectable antipsychotics (LAIs) in schizophrenia is usually restricted to patients in long-term treatment, who prefer them to oral antipsychotics, and to patients with multiple relapses who have a history of non-adherence. However, preliminary evidence from patients in the early phases of the disease suggest that second generation LAIs may be superior to second generation oral medications with regard to the control of negative symptoms and psychosocial functioning. Moreover, several studies have found that psychiatrists are generally reluctant to prescribe LAI antipsychotics and under-estimate their acceptability by patients. Key elements to take into account when offering a LAI in the early course of schizophrenia should include their potential superiority in allowing early detection of non-adherence and in reducing the number of rehospitalisations and relapses.

Conclusioni

- *La schizofrenia è un disturbo che richiede un trattamento il più precoce possibile*
- *La presa in carico nel lungo termine complessiva e una strategia integrata di interventi clinici e psicosociali appare fondamentale per il raggiungimento di una condizione di recovery*
- *Il mantenimento della terapia farmacologica a lungo termine sin dal primo episodio appare fondamentale per tale obbiettivo*