Psicosi e abuso di sostanze: possibili opportunità terapeutiche

GIANCARLO CERVERI MD PHD

DIRETTORE DSMD ASST LODI

MILANO, 30.01.2020

Summary

- Manifestazioni cliniche e implicazioni diagnostiche su decorso e prognosi di psicosi e SUD
- Alcune riflessioni sulle opportunità terapeutiche
- Le implicazioni organizzative

Quali le concettualizzazioni per il rapporto tra SUD e Patologia Psichica

Beyond the "at risk mental state" concept: transitioning to transdiagnostic psychiatry

Patrick D. McGorry, Jessica A. Hartmann, Rachael Spooner, Barnaby Nelson

Orygen, The National Centre of Excellence in Youth Mental Health, and Centre for Youth Mental Health, University of Melbourne, Parkville, Australia

The "at risk mental state" for psychosis approach has been a catalytic, highly productive research paradigm over the last 25 years. In this paper we review that paradigm and summarize its key lessons, which include the valence of this phenotype for future psychosis outcomes, but also for comorbid, persistent or incident non-psychotic disorders; and the evidence that onset of psychotic disorder can at least be delayed in ultra high risk (UHR) patients, and that some full-threshold psychotic disorder may emerge from risk states not captured by UHR criteria. The paradigm has also illuminated risk factors and mechanisms involved in psychosis onset. However, findings from this and related paradigms indicate the need to develop new identification and diagnostic strategies. These findings include the high prevalence and impact of mental disorders in young people, the limitations of current diagnostic systems and risk identification approaches, the diffuse and unstable symptom patterns in early stages, and their pluripotent, transdiagnostic trajectories. The approach we have recently adopted has been guided by the clinical staging model and adapts the original "at risk mental state" approach to encompass a broader range of inputs and output target syndromes. This approach is supported by a number of novel modelling and prediction strategies that acknowledge and reflect the dynamic nature of psychopathology, such as dynamical systems theory, network theory, and joint modelling. Importantly, a broader transdiagnostic approach and enhancing specific prediction (profiling or increasing precision) can be achieved concurrently. A holistic strategy can be developed that applies these new prediction approaches, as well as machine learning and iterative probabilistic multimodal models, to a blend of subjective psychological data, physical disturbances (e.g., EEG measures) and biomarkers (e.g., neuroinflammation, neural network abnormalities) acquired through fine-grained sequential or longitudinal assessments. This strategy could ultimately enhance our understanding and ability to predict the onset, early course and evolution of mental ill health, further opening pathways for preventive interventions.

Key words: At risk mental state, psychosis, ultra high risk, transition, transdiagnostic psychiatry, clinical staging, CHARMS, prediction strategies, network theory, dynamical systems theory, joint modelling

(World Psychiatry 2018;17:133–142)

Da un modello di diagnosi precoce per la Schizofrenia…

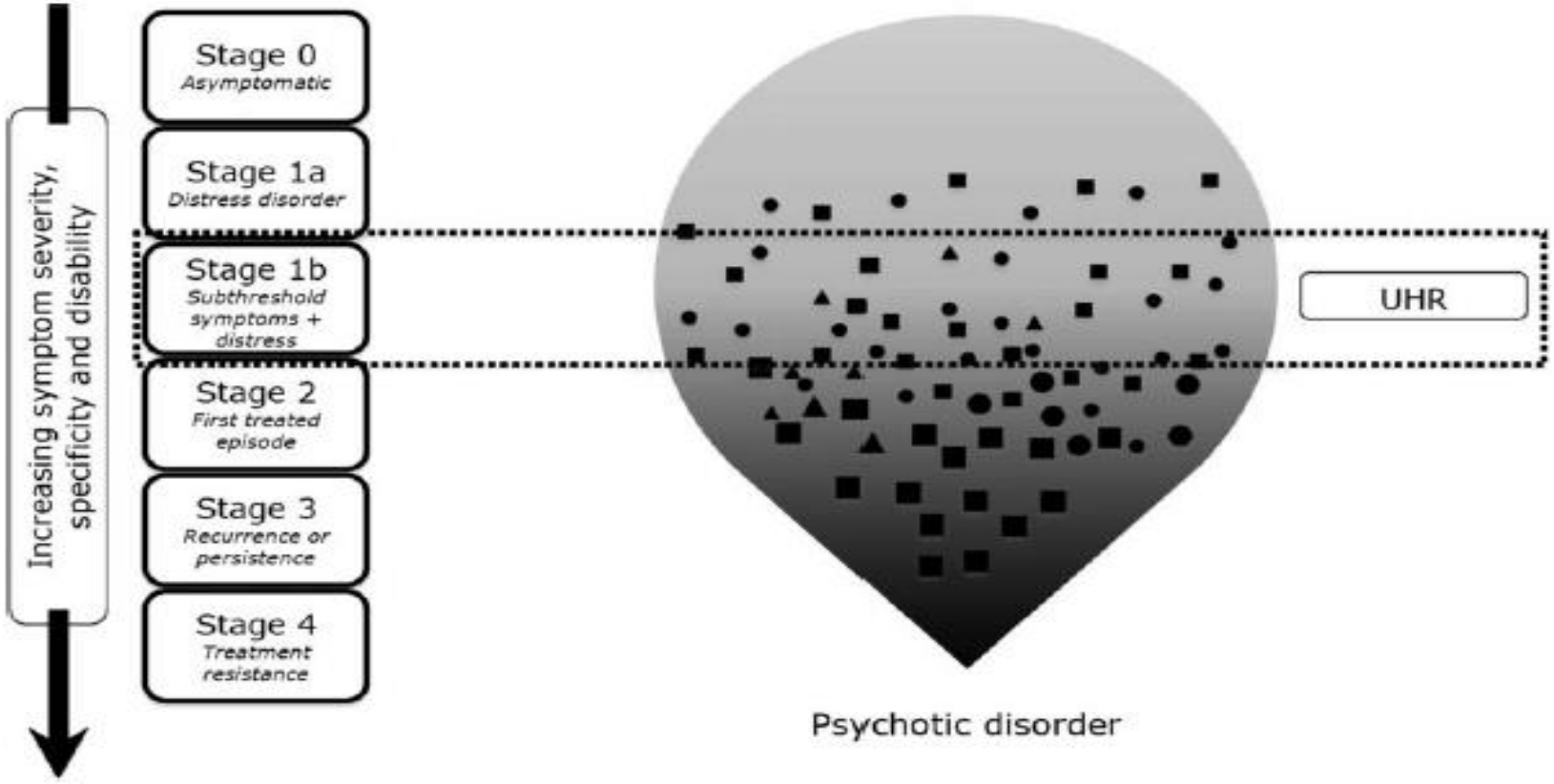


Figure 1 Traditional ultra high risk (UHR) paradigm in the context of clinical staging. The shapes represent different types of symptoms

Ad un modello rivolto a "Stati Mentali a Rischio"

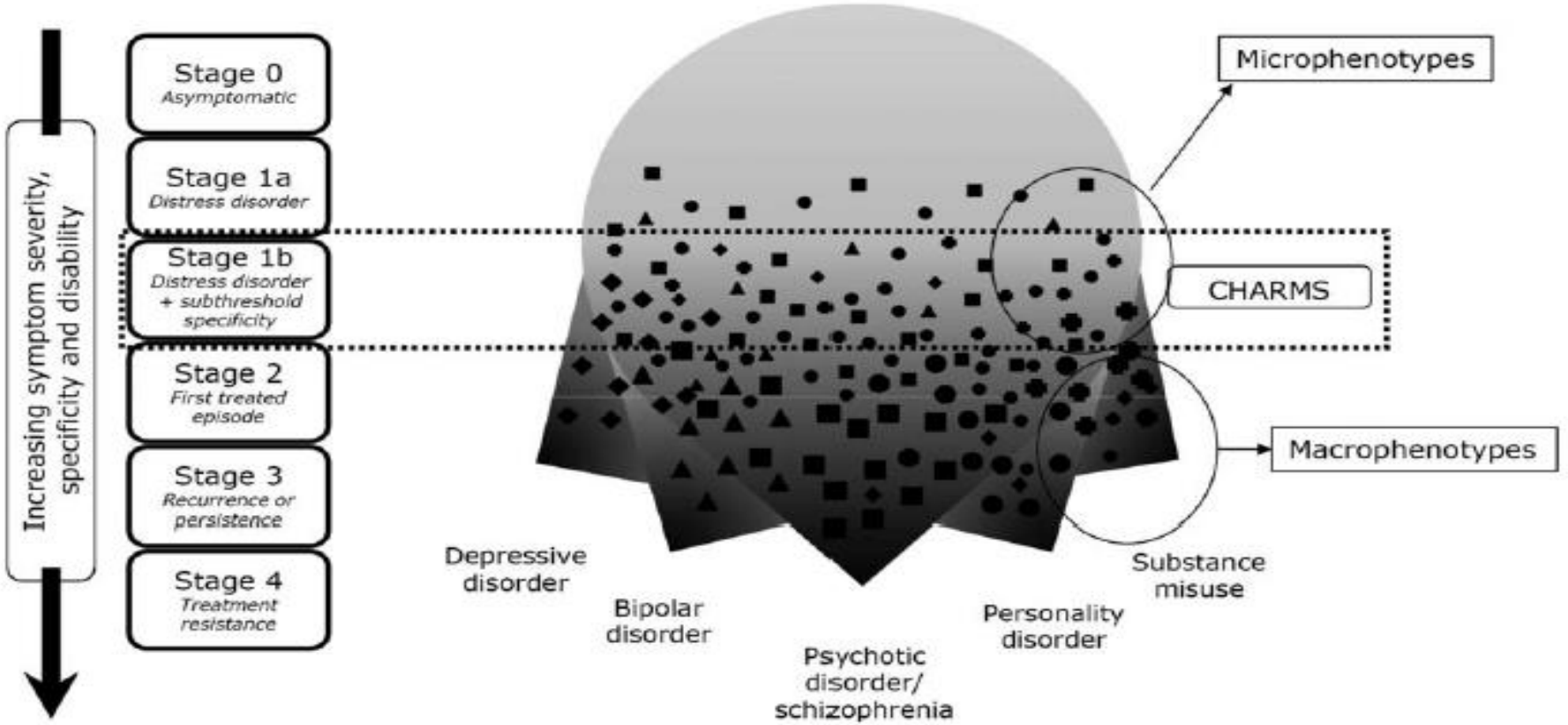


Figure 2 New transdiagnostic Clinical High At Risk Mental State (CHARMS) paradigm in the context of clinical staging. The shapes represent different types of symptoms

Research

JAMA Psychiatry | Original Investigation

Association of Substance Use Disorders With Conversion From Schizotypal Disorder to Schizophrenia

Carsten Hjorthøj, PhD, MSc; Nikolai Albert, PhD, MD; Merete Nordentoft, DrMedSci, PhD, MD

JAMA Psychiatry. 2018;75(7):733-739. doi:10.1001/jamapsychiatry.2018.0568
Published online April 25, 2018.

One-quarter to one-half of patients with schizotypal disorder experience conversion to schizophrenia within 5 years. …Substance use disorders are common in patients with schizotypal disorder, and cannabis has been shown to be a risk factor for developing schizotypal disorder. Cannabis has also been linked to an increased risk of schizophrenia. Other substance use disorders, in particular alcohol use disorder, may also increase risk of later schizophrenia.

Gli effetti delle sostanze sul decorso della patologia psichica

Uno studio di coorte prospettico condotto dal 1981 al 2014 su soggetti con Disturbo Schizotipico di personalità.

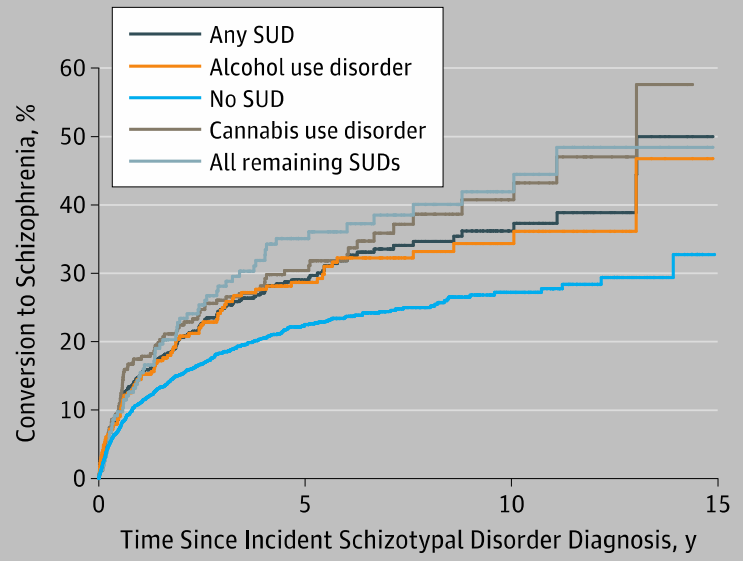
2539 partecipanti (1448 uomini [57.0%] e 1091 donne [43.0%].

Dopo 2 anni 16.3% vanno incontro a conversione a schizofrenia, Dopo 20 anni il tasso di conversione è stato 33.1% nella popolazione totale e 58.2% tra coloro che avevano un disturbo da uso di cannabis.

Hjorthøj et al., *JAMA Psychiatry*. 2018;75(7):733-739

Diverse sostanze diversi effetti

Figure. Conversion Rates From Schizotypal Disorder to Schizophrenia



No. at risk				
Any SUD	504	219	60	6
Alcohol use disorder	261	124	38	4
No SUD	2028	690	210	37
Cannabis use disorder	244	99	26	4
All remaining SUDs	154	68	24	<4[a]

Includes 2539 participants. Data are stratified by substance use disorder (SUD) categories. Numbers do not add up to 2539 because a single person can have more than 1 type of SUD.

[a] Danish law does not allow us to give counts of less than 4 from registers.

Hjorthøj et al., *JAMA Psychiatry*. 2018;75(7):733-739

Uso di sostanze e decorso

Un campione di 195 pazienti inseriti in First Treatment Programme per psicosi, valutati per funzionamento neurocognitivo a 1, 2, 5 e 10 anni.
Gli indici valutati motor speed, verbal learning, visuomotor processing, verbal fluency, and executive functioning.
Pazienti valutati su 4 gruppi basati sui pattern di uso di sostanze nei primi 2 anni di trattamento: persistent users, episodic users, stop-users, and nonusers.

Melissa A. Weibell et al., 2019

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 12 July 2019
doi: 10.3389/fpsyt.2019.00495

Early Substance Use Cessation Improves Cognition—10 Years Outcome in First-Episode Psychosis Patients

Melissa A. Weibell[1,2], Jan Olav Johannessen[1,2], Bjørn Auestad[3,4], Jørgen Bramness[5,6], Kolbjørn Brønnick[1], Ulrik Haahr[4], Inge Joa[1,2], Tor Ketil Larsen[1,7], Ingrid Melle[6,8], Stein Opjordsmoen[6,8], Bjørn Rishovd Rund[9,10], Jan Ivar Røssberg[6,8], Erik Simonsen[11,12], Per Vaglum[13], Helen Stain[14], Svein Friis[6,8] and Wenche ten Velden Hegelstad[1]*

[1] TIPS Centre for Clinical Research in Psychosis, Division of Psychiatry, Stavanger University Hospital, Stavanger, Norway, [2] Faculty of Health, University of Stavanger, Stavanger, Norway, [3] Department of Mathematics and Physics, University of Stavanger, Stavanger, Norway, [4] Research Department, Stavanger University Hospital, Stavanger, Norway, [5] Norwegian National Advisory Unit on Concurrent Substance Abuse and Mental Health Disorder, Innland Hospital Trust, Hamar, Norway, [6] Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway, [7] Institute of Psychiatry, University of Bergen, Bergen, Norway, [8] Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway, [9] Department of Psychology, University of Oslo, Oslo, Norway, [10] Vestre Viken Hospital Trust, Drammen, Norway, [11] Psychiatric Research Unit, Psychiatry Region Zealand, Slagelse, Denmark, [12] Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark, [13] Department of Behavioural Sciences in Medicine, University of Oslo, Oslo, Norway, [14] School of Social and Health Sciences, Leeds Trinity University, Leeds, United Kingdom

OPEN ACCESS

Edited by:
Silvio Bellino, University of Turin, Italy

Reviewed by:
Kelly Anne Allott, University of Melbourne, Australia
Szabolcs Keri, University of Szeged, Hungary

***Correspondence:**
Melissa Weibell
weim@sus.no

Specialty section:
This article was submitted to Psychopathology, a section of the journal Frontiers in Psychiatry

Received: 30 October 2018
Accepted: 24 June 2019
Published: 12 July 2019

Citation:
Weibell MA, Johannessen JO, Auestad B, Bramness J, Brønnick K, Haahr U, Joa I, Larsen TK, Melle I, Opjordsmoen S, Rund BR, Røssberg JI, Simonsen E, Vaglum P, Stain H, Friis S and Hegelstad WtV (2019) Early Substance Use Cessation Improves Cognition—10 Years Outcome in First-Episode Psychosis Patients. Front. Psychiatry 10:495. doi: 10.3389/fpsyt.2019.00495

Background: Cognitive impairment may be a risk factor for, as well as a consequence of, psychosis. Non-remitting symptoms, premorbid functioning, level of education, and socioeconomic background are known correlates. A possible confounder of these associations is substance use, which is common among patients with psychosis and linked to worse clinical outcomes. Studies however show mixed results for the effect of substance use on cognitive outcomes. In this study, the long-term associations of substance use with cognition in a representative sample of first-episode psychosis patients were examined.

Methods: The sample consisted of 195 patients. They were assessed for symptom levels, function, and neurocognition at 1, 2, 5, and 10 years after first treatment. Test scores were grouped into factor analysis-based indices: motor speed, verbal learning, visuomotor processing, verbal fluency, and executive functioning. A standardized composite score of all tests was also used. Patients were divided into four groups based on substance-use patterns during the first 2 years of treatment: persistent users, episodic users, stop-users, and nonusers. Data were analyzed using linear mixed effects modeling.

Results: Gender, premorbid academic functioning, and previous education were the strongest predictors of cognitive trajectories. However, on motor speed and verbal learning indices, patients who stopped using substances within the first 2 years of follow-up improved over time, whereas the other groups did not. For verbal fluency, the longitudinal course was parallel for all four groups, while patients who stopped using substances demonstrated superior performances compared with nonusers.

Risultati

- Persistent and EUs had poorer premorbid academic functioning and were more likely to be male. However, both male gender and poor premorbid adjustment represent poor prognostic factors in psychosis. Thus, it may be challenging to disentangle the effect of poor premorbid adjustment from substance use.
- The present study demonstrated differences in motor speed and verbal indices in patients who discontinued substance use early on in their course of treatment. This, as well as previous published results indicating that SUs reach levels as good as or better than NUs, conveys a powerful message to clinicians

Melissa A. Weibell et al., 2019

Una sintesi parziale

Se è presente abuso di sostanze:

1) Il decorso è peggiore aumenta il rischio di transizione
2) Se non si sospende il danno nel tempo è più rilevante sul funzionamento globale

Psychiatry Research 268 (2018) 303–311

Contents lists available at ScienceDirect

Psychiatry Research

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

Impact of comprehensive treatment for first episode psychosis on substance use outcomes: A randomized controlled trial

Corinne Cather[a,*], Mary F. Brunette[b], Kim T. Mueser[c], Steven F. Babbin[d], Robert Rosenheck[e], Christoph U. Correll[f], Piper Kalos-Meyer[g]

[a] Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
[b] Department of Psychiatry, Dartmouth College Geisel School of Medicine, Concord, NH, USA
[c] Boston University Center for Psychiatric Rehabilitation, Boston University, Boston, MA, USA
[d] Office of Institutional Research and Evaluation, Tufts University, Medford, MA, USA
[e] Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA
[f] Department of Psychiatry, The Feinstein Institute for Medical Research and The Zucker Hillside Hospital, Manhasset, NY, USA
[g] Department of Psychiatry, University of Minnesota, Minneapolis, MN USA

Quali possibilità di successo con un trattamento integrato?

Il Disegno dello studio

- 404 soggetti arruolati nel programma Recovery After an Initial Schizophrenia Episode (RAISE)-Early Treatment Program (ETP).
- Assegnati ramdom ad un intervento di 2 anni NAVIGATE (n = 223) or usual care (n = 181) valutati mensilmente per substance use .
- At baseline, over one-half (51.7%) of the participants met criteria for a lifetime SUD, including over one-third with alcohol use disorder (36.4%) and with cannabis use disorder (34.7%).

Cather et al ., 2018

Le caratteristiche dell'intervento

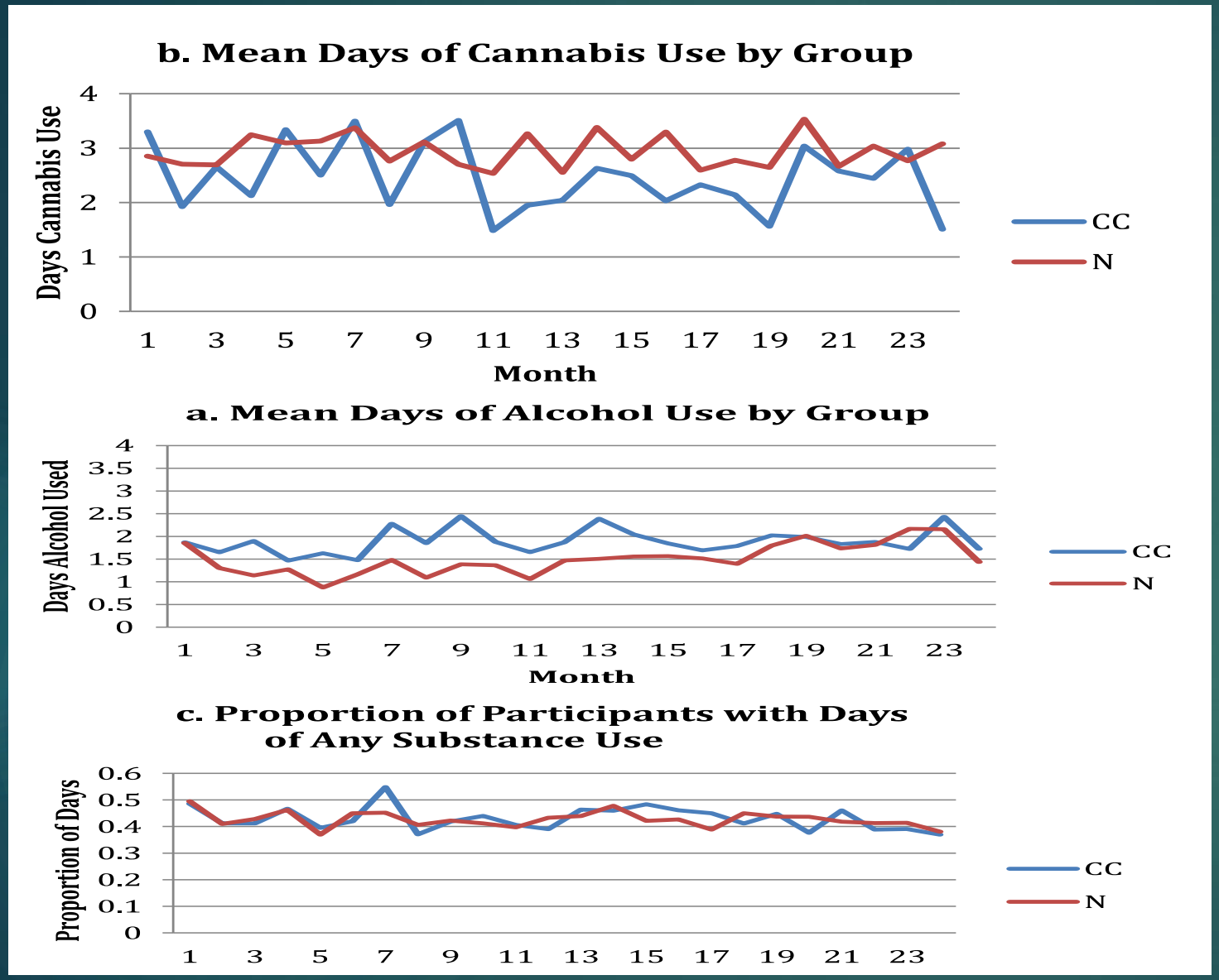
The NAVIGATE program is a standardized, team-based intervention specifically designed to be implemented in the context of typical community mental health center treatment provided in the U.S. healthcare system (Mueser et al., 2015). The program was implemented by a **multidisciplinary team.** The team was usually comprised of **five clinicians** who provided **four different interventions** in an integrated fashion: **individualized medication treatment, family psychoeducation, supported employment and education, and individual resiliency training** (IRT).

Cather et al ., 2018

I risultati dell'intervento

Comprehensive interviews were conducted at baseline and every 6 months, which were supplemented by brief monthly phone each month, for two years. Study background and primary findings have been published elsewhere (Kane et al., 2016; Kane et al., 2015). Compared to study participants at the CC sites, participants at NAVIGATE sites had **higher rates of retention in treatment, greater reductions in symptoms, and more improvement in quality of life, interpersonal relationships, and involvement in work or school**

Cather et al ., 2018



Gli effetti sul consumo di alcohol e sostanze

CATHER ET AL ., 2018

Le conclusioni degli autori

- Lo studio non era focalizzato sul SUD
- La valutazione dei consumi di alcol e sostanze derivava da self-report

Concludono…

In summary, this study demonstrated that the comprehensive NAVIGATE program did not lead to greater reductions in substance use over a two-year study period compared to usual community care for young people with FEP.

Early Intervention in Psychiatry. 2020;14:69–79. wileyonlinelibrary.com/journal/eip

Received: 22 September 2018 | Revised: 11 January 2019 | Accepted: 14 April 2019

DOI: 10.1111/eip.12826

Check for updates

WILEY

ORIGINAL ARTICLE

Long-acting antipsychotic medication as first-line treatment of first-episode psychosis with comorbid substance use disorder

Amal Abdel-Baki[2,3] | Dominic Thibault[2] | Sofia Medrano[2] | Emmanuel Stip[2,3] | Martin Ladouceur[1] | Ramzan Tahir[1] | Stephane Potvin[2,4]

Esistono modalità di trattamento più efficaci di altre? Uno studio su soggetti con FEP e SUD

Il disegno dello studio

- Studio Naturalistico. Longitudinale, retrospettivo e prospettico (3 anni)
- 237 con FEP e SUD soggetti trattati nei 2 servizi di intervento precoce per psicosi a Montreal dal 2005 al 2012.
- Gli interventi: «5 years of specialized EIS according to international guidelines (Orygen, 2016), including pharmacological and intensive recovery-oriented psychosocial interventions with case-management, group and individual psycho-education for relapse prevention, cognitive behavioural and motivational interventions and family interventions.»
- Suddivisi per modalità di trattamento iniziale introdotto: oral antipsychotics (OAP, n = 206) o LAI-AP (n = 31).

Abdel-Baki et al, 2018

Le caratteristiche dei due Gruppi

- Patients treated with LAI-AP first (n = 31) or OAP first (n = 206) were **similar on the majority of their baseline characteristics**.
- Patients of the LAI-AP first were **less likely to be financially autonomous** (32.3% of LAI-AP first group compared to 64.5% for OAP first; P < 0.001) and **more likely** to have experienced **homelessness** (38.7% for LAI-AP first compared to 20.0% for OAP first; P = 0.037).
- The LAI-AP first group also had a **higher mean PANSS general psychopathology** score at admission (39.5 for LAI-AP first compared to 34.8 for OAP first; P = 0.011).

Abdel-Baki et al, 2018

Clinical data	LAI-AI first (n = 31)	OAP first (n = 206)	*P*-value
PANSS, mean (s.d)			
Positive symptoms	20.4 (5.2)	19.6 (5.6)	0.608
Negative symptoms	23.0 (3.8)	22.7 (5.6)	0.312
General symptoms	39.5 (5.2)	34.8 (6.4)	*0.011*
CDS, mean (s.d)	7.0 (3.5)	5.6 (3.8)	0.206
CGI, mean (s.d)	4.9 (0.6)	4.9 (0.9)	0.774
Substance use disorder, n (%)	28.0 (90.3)	188.0 (91.3)	0.864
Alcohol	11.0 (35.5)	67.0 (32.5)	0.903
Cannabis	25.0 (80.6)	163.0 (79.1)	0.846
Cocaine	2.0 (6.5)	27.0 (13.1)	0.447
Amphetamines	6.0 (19.4)	48.0 (23.3)	0.796

Functional data	LAI-AI first (n = 31)	OAP first (n = 206)	*P*-value
GAF best in lifetime, mean (s.d.)	58.6 (10.1)	60.7 (11.2)	0.290
GAF, mean (s.d.)	27.4 (8.7)	29.32 (10.0)	0.274
SOFAS, best in lifetime, mean (s.d.)	59.5 (8.9)	60.6 (11.1)	0.542
SOFAS, mean (s.d)	30.1 (11.8)	32.7 (12.5)	0.285
QLS, mean (s.d)	47.2 (15.1)	49.4 (22.9)	0.662

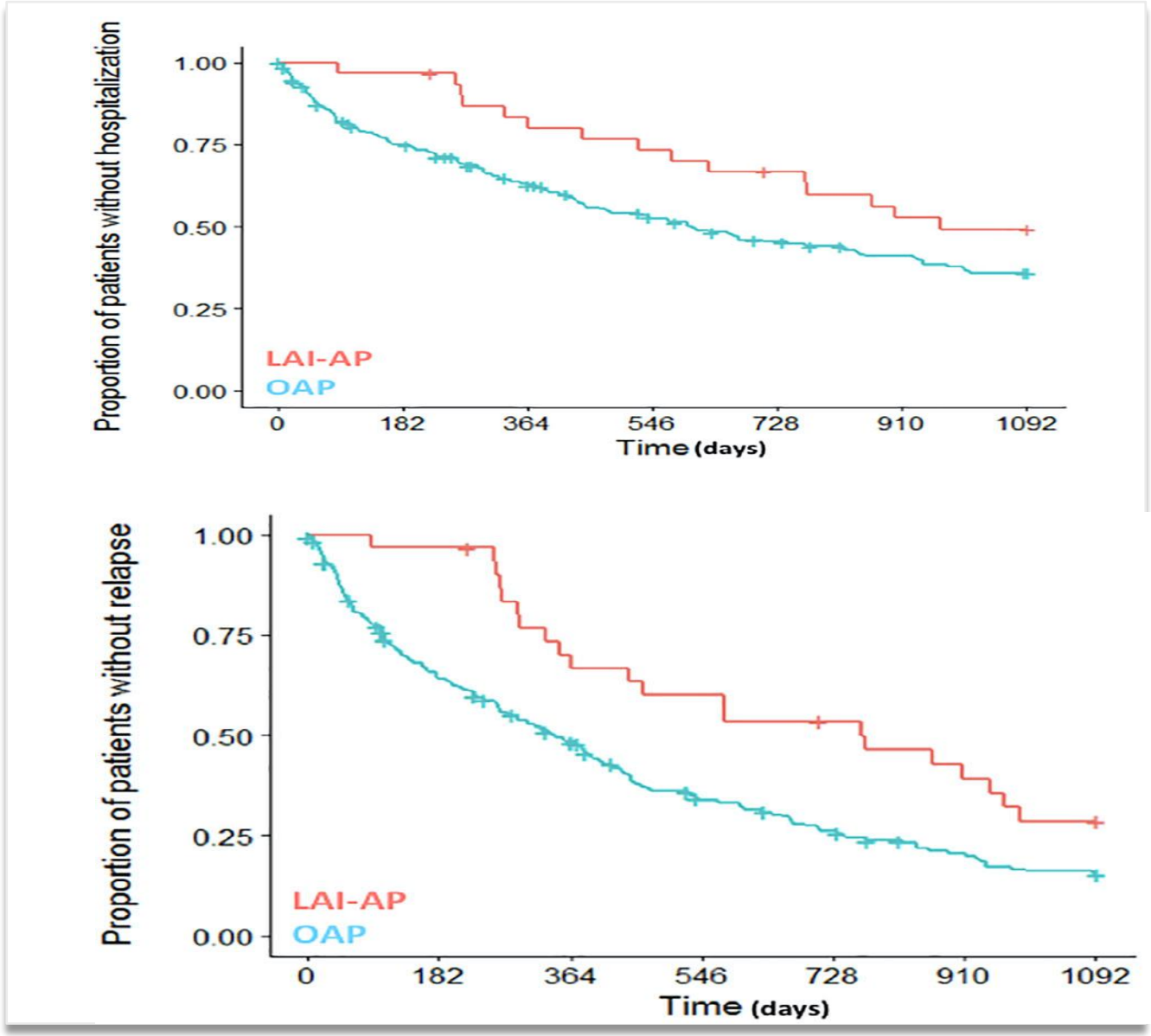
Le caratteristiche cliniche dei due campioni

ABDEL-BAKI ET AL, 2018

Outcome

- Hospitalization and psychotic relapse defined as an **exacerbation of clinical symptoms requiring either an adjustment in medication, an increase in the intensity of outpatient services.**
- During the 3-year follow-up period, **75.5% of patients experienced at least one psychotic relapse** and **52.1% were rehospitalized** at least once because of a relapse.

Abdel-Baki et al, 2018



Recidiva e riospedalizzazione nei due gruppi

Abdel-Baki et al, 2018

Quali risultati?

Abdel-Baki et al, 2018

- In the LAI-AP first group, **67.7%** experienced at least one relapse during the study period compared to **76.7%** in the OAP.
- The mean time-to-first relapse was **694 days for the LAI-AP** first group compared to **447 days in the OAP first** group (P = 0.008).
- The differences in first rehospitalization rates (48.4% and 57.3%, respectively) and time-to- first rehospitalization (813 and 619 days, respectively; P = 0.065) between the LAI-AP first and OAP first groups were not statistically significant.

frontiers in Psychiatry

CLINICAL TRIAL
published: 19 September 2019
doi: 10.3389/fpsyt.2019.00656

Check for updates

Paliperidone Extended-Release Tablets for the Treatment of Methamphetamine Use Disorder in Chinese Patients After Acute Treatment: A Randomized, Double-Blind, Placebo-Controlled Exploratory Study

Gang Wang[1†], Li Ma[1†], Xuebing Liu[1], Xue Yang[1], Sheng Zhang[1], Yongde Yang[1], Zaifeng Xu[1] and Wei Hao[2]*

[1] Drug Abuse Ward, Wuhan Mental Health Center, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [2] Department of Psychiatry & Mental Health Institute of the Second Xiangya Hospital, Central South University, National Clinical Research Center on Mental Disorders & National Technology Institute on Mental Disorders, Hunan Key Laboratory of Psychiatry and Mental Health, Changsha, China

OPEN ACCESS

Edited by:
Min Zhao,
Shanghai Mental Health Center (SMHC), China

Gli antipsicotici sono utili al trattamento dei soggetti con abuso di sostanze? (ovvero paliperidone in Meth Use Disorder)

Alcuni dati

- L'uso di METH può contribuire all'insorgenza di psicosi. Allucinazioni e deliri sono riportati in METH users nel 10-60% dei casi ed sono associati a rischio di comportamenti violenti.
- Più del 50% dei soggetti dopo trattamento in acuto tende a recidivare con alta probabilità di ricorrenza di sintomi psicotici.
- METH porta ad un eccessivo rilascio dopaminergico sottocorticale e può indurre sesitivizzazione comportamentale che si ritiene sia la causa della MAP.

Brecht ML, Herbeck D. Time to relapse following treatment for methamphetamine use: a long-term perspective on patterns and predictors. *Drug Alcohol Depend* (2014) 139:18–25.
Grant KM, LeVan TD, Wells SM, Li M, Stoltenberg SF, Gendelman HE, et al. Methamphetamine-associated psychosis. *J Neuroimmune Pharmacol* (2012) 7(1):113–39. doi: 10.1007/s11481-011-9288-1

Il disegno dello studio

Double-blind, placebo-controlled, randomized exploratory trial in METH-dependent adults with METH-associated psychosis (MAP).

- Dopo le dimissioni ospedaliere e 7 giorni senza terapia 80 soggetti vengono assegnati a uno dei due gruppi (paliperidone ER 3 mg o placebo).
- I partecipanti fornivano un campione di urine alla settimana e ricevevano un trattamento di counseling.

Wang et al., 2019

Risultati -1: sintomi psicotici e craving

Ricorrenza sintomi psicotici: minor rischio di ricorrenza nei soggetti trattati con paliperidone, (HR = 0.15, p = 0.003), maggior durata di astinenza da METH è associata a a minor rischio ricorrenza (HR = 0.93, p < 0.001).

Methamphetamine Cravings: Paliperidone ER risulta associato ad un significativo miglioramento nel METH craving score.

TABLE 2 | The Cox model measured the hazard ratio and 95% confidence intervals of psychotic symptom relapse associated with treatment.

Variable	HR	95% CI	*p* value
Group	0.15	0.04–0.52	0.003
Duration of METH abstinence	0.93	0.91–0.96	<0.001

Group includes paliperidone ER and placebo; HR, hazard ratio; CI, confidence.

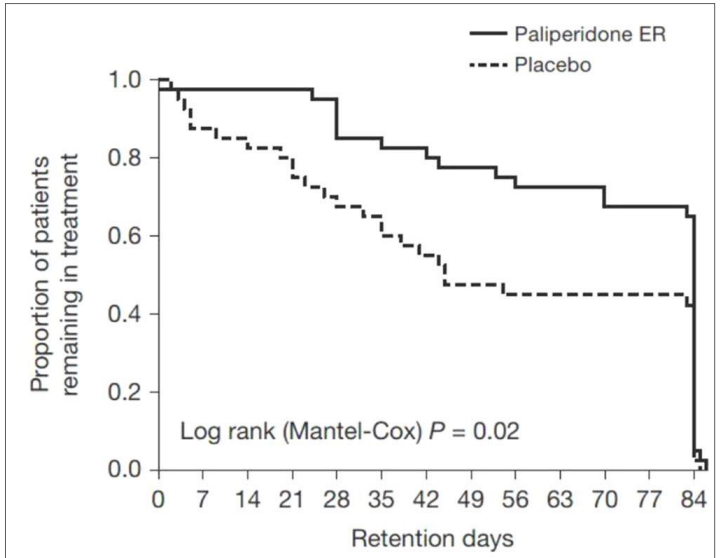
Wang et al., 2019

Risultati -2: Treatment Retention and Medication Adherence

56% dei pazienti hanno completato il trial (45/80)

Placebo group mostra una retention significativamente inferiore [51.5 days; 95% (CI), 41.6–61.4] rispetto al gruppo paliperidone ER (69.4 days; 95% CI, 61.9–76.9; p = 0.02),

Self- reported adherence was 76% in the paliperidone ER group and 68% in the placebo group (p = 0.07).



ER = extended release.

FIGURE 2 | Proportion of patients remaining in treatment.

Wang et al., 2019

Risultati -3: Urine Drug Screen Results

- Nello studio sono stati raccolti 705 test urine.
- 255 su 960 (26.6%) sono missing, 76 (15.8%) nel gruppo paliperidone ER e 179 (37.3%) nel gruppo placebo.
- Tutti i missing samples sono dovuti al termine anticipato dello studio.
- Non ci sono differenze significative tra i due gruppi per la positività al test 27.5% (n = 11) dei pazienti nel gruppo paliperidone e 32.5% (n = 13) in quelli con placebo.

Wang et al., 2019

Safety and Tolerability

- Solo una paziente con paliperidone ha discontinuato per amenorrea.
- Gli eventi avversi riportati includevano akathisia (paliperidone ER: 6/40 o 15%; placebo: 2/40 or5%; P = 0.1), insonnia (paliperidone ER: 17/40 or 42.5%; placebo: 21/40 or 52.5%; P = 0.3), e agitazione (paliperidone ER: 18/40 or 45%; placebo: 23/40 or 57.5%; P = 0.3).
- At the study completion, participants were asked to guess their treatment assignment. There was no evidence of unblinding: 19/40 (48%) in the paliperidone ER group and 22/40 (55%) in the placebo group guessed correctly (p = 0.5).

Wang et al., 2019

Alcune riflessioni sullo studio

- Therefore, the **reduction in the risk of psychotic recurrence** in our study with paliperidone ER was significant for the treatment of METH use disorder.
- We did not find evidence for paliperidone ER **reducing METH use in METH dependence** compared to placebo.
- We included subjects with MAP history but without current psychotic symptoms and METH use after detoxification.

Wang et al., 2019

Esistono altre vie di trattamento?

Journal of
Clinical Medicine

MDPI

Review

The Potential of Cannabidiol as a Treatment for Psychosis and Addiction: Who Benefits Most? A Systematic Review

Albert Batalla [1,*,†], Hella Janssen [1,†], Shiral S. Gangadin [1,2] and Matthijs G. Bossong [1]

1 Department of Psychiatry, UMC Utrecht Brain Center, University Medical Center Utrecht, 3508 GA Utrecht, The Netherlands
2 Section of Neuropsychiatry, Department of Biomedical Sciences of Cells and Systems, University Medical Center Groningen, 9713 AV Groningen, The Netherlands
* Correspondence: abatallacases@gmail.com; Tel: +31-(0)88-755-8180
† These authors contributed equally to this work.

Received: 24 June 2019; Accepted: 18 July 2019; Published: 19 July 2019

check for updates

Il cannabidiolo come trattamento?

Esiste un ruolo dei cannabinoidi nella schizofrenia?

- I recettori per cannabinoidi sono presenti soprattutto in strutture corticali e limbiche. Il sistema degli eCB risulta essere un sistema a messaggero retrogrado che regola sia l'attività eccitatoria glutamatergica che quella inibitoria GABAergica.
- Il ruolo del sistema eCB nella patofisiologia della schizofrenia è stata suggerito da una serie di evidenze in continuo accumulo.

Katona, I.; Freund, T.F. Multiple Functions of Endocannabinoid Signaling in the Brain. *Annu. Rev. Neurosci.* **2012**, *35*, 529–558.
Bossong, M.G.; Niesink, R.J.M. Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia. *Prog. Neurobiol.* **2010**, *92*, 370–385. [

CBD come trattamento?

- Mentre il THC è associato ad aumentato rischio di sviluppo di schizofrenia e SUD, CBD potrebbe avere effetti positivi su sintomi psicotici e cognitivi indotti dalla somministrazione acuta di THC.
- CBD potrebbe diminuire il rischio di psicosi associato a THC, per questo motivo mostra un profilo interessante come nuovo agente antipsicotico.
- Alcuni dati suggeriscono un effetto sulla riduzione degli effetti da sospensione ed un effetto sulla riduzione dell'utilizzo.

Chye, Y.; Christensen, E.; Solowij, N.; Yücel, M. The Endocannabinoid System and Cannabidiol's Promise for the Treatment of Substance Use Disorder. *Front. Psychiatry* **2019**, *10*.
Iseger, T.A.; Bossong, M.G. A systematic review of the antipsychotic properties of cannabidiol in humans. *Schizophr. Res.* **2015**, *162*, 153–161.

I dati di letteratura sulla psicosi

Table 1. Case reports and clinical trials on the efficacy of cannabidiol (CBD) as a treatment for psychotic disorders.

Study	Study Design	Participants	Substance Use	Intervention	CBD Administration	Primary Outcomes
Zuardi et al. (1995) [51]	Case report	19-year-old female schizophrenia inpatient (two years after first hospitalization)	Not reported	Progressive in monotherapy c followed by halo		Treatment with either CBD or amisulpride is associated with improvement of symptomatology, but CBD has a superior side-effect profile.
Zuardi et al. (2006) [52]	Case series	Three male inpatients with treatment-resistant schizophrenia	Not reported	Progressive in monotherapy c followed by olan		
Makiol and Klunge (2019) [53]	Case report	57-year old-female treatment-resistant schizophrenia inpatient	Not reported	Treatment with C clozapine an		Improvement of symptomatology, no side effects.
Leweke et al. (2012) [54]	Double-blind CBD vs. amisulpride RCT	39 acutely psychotic inpatients	Not reported, exclusion criteria were SUD or positive urine drug screening for illicit drugs in general and cannabis in particular.	Hospitalizatior treatment with Cl		
McGuire et al. (2018) [55]	Double-blind placebo RCT	88 outpatients with schizophrenia	Not reported, substance use was not an exclusion and not prohibited during the study.	A six-week trea adjunctive to medi		CBD 300 mg and placebo both improved cognitive performance as compared to CBD 600 mg. No effects on symptomatology.
Hallak et al. (2010) [56]	Single dose double-blind placebo RCT	28 schizophrenia outpatients	Not reported	Acute treatment of C		
Boggs et al. (2018) [57]	Double-blind placebo RCT	36 outpatients with chronic schizophrenia	Not reported, patients with substance abuse in the past three months or dependence in the past six months were excluded.	Six-week treatmer to a stable dose medi		Cognitive performance improved after placebo, symptomatology improved in both groups, no differences between groups.

CBD: Cannabidiol; RCT: Randomized clinical tria

I dati di letteratura su SUD

Table 2. Case reports and clinical trials on the efficacy of CBD as a treatment for substance use disorders.

Study	Study Design	Participants	Intervention	CBD Administration	Primary Outcomes
Allsop et al. (2014) [58]	Double-blind placebo RCT	51 inpatients with cannabis dependence	A six	Sativex reduced cannabis withdrawal and cravings, and improved treatment retention rates.	
Trigo et al. (2016) [59]	Double-blind placebo RCT	Nine individuals with cannabis dependence	Eigh		
Trigo et al. (2018) [60]	Double-blind placebo RCT	27 individuals with cannabis dependence	Twelv	During interruption of cannabis use both fixed and titrated doses of Sativex reduced cannabis withdrawal symptoms (but not craving), however the high fixed dose seemed the most effective.	
Crippa et al. (2013) [61]	Case report	19-year-old female diagnosed with cannabis dependence	Hosp		
Shannon and Opila-Lehman (2015) [62]	Case report	27-year-old male diagnosed with bipolar disorder and cannabis dependence	Treat		
Solowij et al. (2018) [63]	Open-label clinical trial	20 ongoing cannabis users		Cannabis use, cravings, and withdrawal decreased in both groups over time. Sativex reduced cannabis cravings.	
Morgan et al. (2013) [64]	Double-blind placebo RCT	24 individuals who smoked >10 cigarettes per day and intended to quit	O		
Hindocha et al. (2018) [65]	Single dose double-blind placebo RCT	30 individuals with tobacco dependence	Treatment with a single dose of CBD after an overnight of cigarette abstinence	Oral; 800 mg CBD	CBD reduced the salience and peasantness of cigarette cues but had no effect on craving and withdrawal.

CBD: Cannabidiol; CBT: Cognitive behavioural therapy; RCT: Randomized clinical trial; THC: Δ9-Tetrahydrocannabinol.

Batalla et al 2019

Studi su psicosi e SUD

Table 3. Studies on CBD treatment for patients with a psychotic disorder and a comorbid cannabis use disorder.

Study	Study Design	Participants	Intervention	CBD Administration	Primary Outcomes
Schipper et al. (2018) [66]	Case report	Seven inpatients with a psychotic disorder and a comorbid treatment-resistant cannabis use disorder	Eight-week treatment with medicinal cannabis (Bedrolite: 0.4% THC and 9% CBD) adjunctive to antipsychotic medication.	Inhalation: 11–45 mg/day	No effect on symptomatology or craving.

CBD: Cannabidiol; THC: Δ 9-tetrahydrocannabinol.

Batalla et al 2019

Quali conclusioni sul CBD

- CBD potrebbe avere alcuni effetti sulla sintomatologia positiva, negativa e cognitiva nella schizofrenia come effetti sul craving e sulla sindrome da sospensione in SUD.
- Le differenze nei disegni sperimentali, la popolazione studiata e i trattamenti concomitanti rendono difficile una corretta interpretazione dei risultati.

Batalla et al 2019

Conclusioni

- Psicosi e SUD un legame conosciuto
- SUD incide sul rischio di ammalare
- SUD peggiora l'outcome della psicosi
- Trattamenti integrati e continuativi sembrano fornire un vantaggio sia per la psicosi che per SUD se si occupano di entrambi le problematiche
- Quali implicazioni per l'organizzazione dei servizi