Utilizzo della Nutraceutica nel trattamento dei Disturbi Psichiatrici

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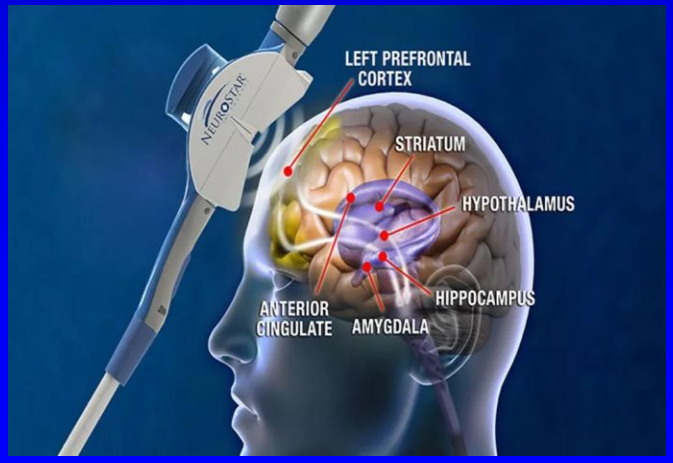
Nuovi Approcci nel trattamento dei Disturbi Psichiatrici



Nutraceutica in Psichiatria: Razionale

- **La società occidentale consuma alimenti altamente lavorati, molto calorici ma poveri di nutrienti. Molte persone sono sovralimentate e malnutrite allo stesso tempo**
- **I meccanismi attraverso i quali la nutrizione può impattare sulla salute mentale sono vari:**
  - Il cervello opera ad un alto tasso metabolico e utilizza una grossa quota di energia e nutrienti
  - Le abitudini alimentari influiscono sul funzionamento del sistema immunitario che influenza il rischio di depressione
  - Le difese antiossidanti, coinvolte nelle patologie mentali, utilizzano cofattori nutrienti
- **Studi epidemiologici e prospettici dimostrano l'impatto della dieta sulla salute mentale**
- **Numerose evidenze supportano il ruolo della supplementazione anche nella gestione delle patologie psichiatriche.**

ISNPR
International Society for Nutritional Psychiatry Research

Conclusions

Present treatment of psychiatric disorders can be improved and greater attention can be given to preventive efforts. As a result of the immense burden of mental disorders, modifiable targets to reduce the incidence of mental disorders are now urgently needed. Diet and nutrition offer key modifiable targets for the prevention of mental disorders, having a fundamental role in the promotion of mental health. Now is time for the recognition of the importance of nutrition and nutrient supplementation in psychiatry. Nutritional medicine should now be considered as a mainstream element of psychiatric practice, with research, education, policy, and health promotion supporting this new framework.

Nutraceutici in Psichiatria: Quando, Come e Perchè

- Quando: nei Disturbi d'Ansia, del Sonno e dell'Umore; quando non via siano condizioni di acuzie o di rischio (storia clinica del paziente, familiarità, etc); quando il medico e il paziente ritengano che vi sia spazio per un intervento di tal genere; in situazioni prodromiche, di residualità, di augmentation

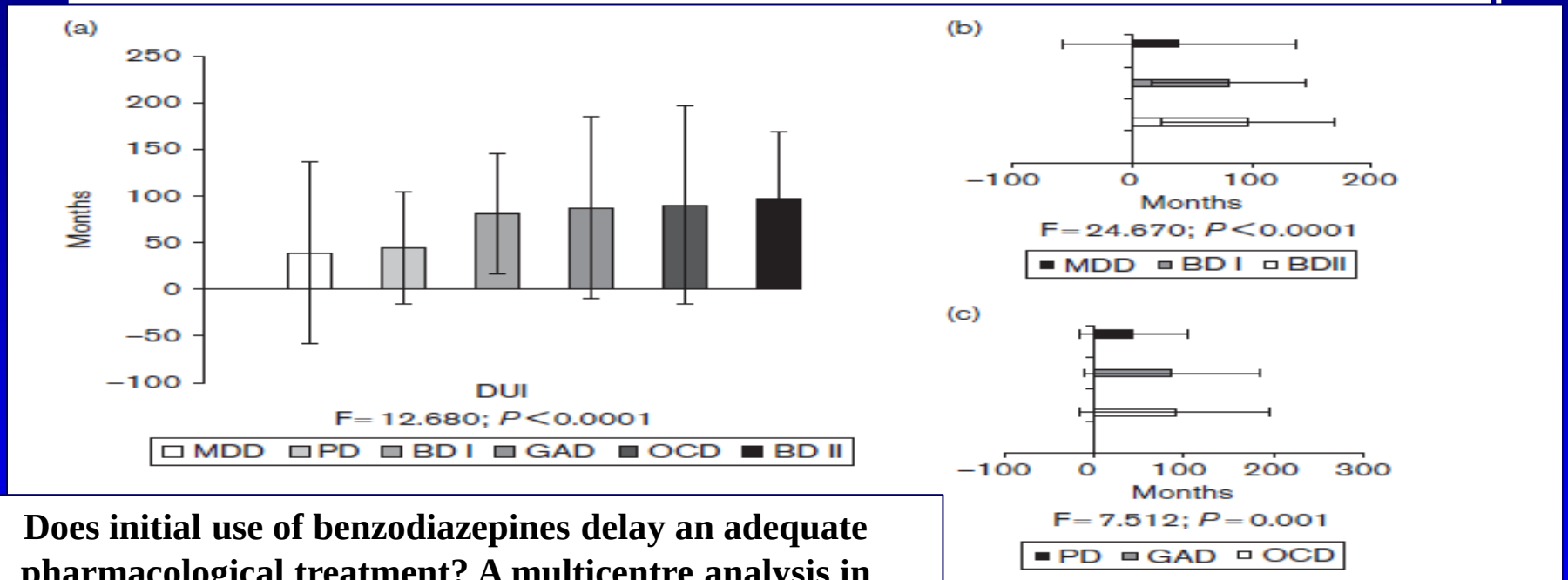
- Perché: per bilanciare l'apporto nutrizionale del paziente; per richiesta del paziente (es., farmacofobia), per risposta parziale del paziente, in determinate condizioni cliniche (rischio di abuso di benzodiazepine, rischio di intossicazione da farmaci), etc.

- Come: con la supervisione del medico/specialista, previa indicazione dei modi e dei tempi, non lasciando il paziente all'autogestione/automedicazione/decisione su come curarsi.

Durata di Malattia Non Trattata nei Disturbi Psichiatrici

Age at onset and latency to treatment (duration of untreated illness) in patients with mood and anxiety disorders: a naturalistic study

Alfredo Carlo Altamura, Massimiliano Buoli, Alessandra Albano and Bernardo Dell'Osso



Does initial use of benzodiazepines delay an adequate pharmacological treatment? A multicentre analysis in patients with Psychotic and Affective Disorders

Dell'Osso et al., Int Clin Psychopharmacol 2018, in press

A. C. Altamura,[1] B. Dell'Osso,[1] E. Mundo,[1] L. Dell'Osso[2]

SUMMARY

Background: Most of the studies on the duration of untreated illness (DUI) as a possible predictor of the clinical outcome and the course have focused on the psychotic disorders. The present naturalistic study was aimed to evaluate the possible relationship between the DUI and some clinical characteristics of a sample of patients with major depressive disorder (MDD). Methods: Sixty-eight patients with MDD, according to the Diagnostic and Statistical Manual of Mental Disorders, IV Edition, Text Revision (DSM-IV-TR) criteria, followed-up for 4 years, were selected, inter-

What's known

Little is known about the relationship between the DUI and major depressive disorder. The role of the DUI, in fact, has been traditionally investigated in psychotic disorders. Nonetheless, it may be of clinical interest to study whether and how a delayed effective treatment, i.e. a longer DUI, may influence the outcome and the course of mood disorders.

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Original article

May duration of untreated illness influence the long-term course of major depressive disorder?

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Available online 14 January 2008

(i) Nutraceutica nei Disturbi Psichiatrici:

tra Letteratura e Linee-Guida

THE LANCET

La crescente importanza della medicina nutrizionale in psichiatria

Nutritional medicine as mainstream in psychiatry

Jerome Sarris, Alan C Logan, Tasnime N Akbaraly, G Paul Amminger, Vicent Balanzá-Martínez, Marlene P Freeman, Joseph Hibbeln, Yutaka Matsuoka, David Mischoulon, Tetsuya Mizoue, Akiko Nanri, Daisuke Nishi, Drew Ramsey, Julia J Rucklidge, Almudena Sanchez-Villegas, Andrew Scholey, Kuan-Pin Su, Felice N Jacka, on behalf of The International Society for Nutritional Psychiatry Research

Psychiatry is at an important juncture, with the current pharmacologically focused model having achieved modest benefits in addressing the burden of poor mental health worldwide. Although the determinants of mental health are complex, the emerging and compelling evidence for nutrition as a crucial factor in the high prevalence and incidence of mental disorders suggests that diet is as important to psychiatry as it is to cardiology, endocrinology, and gastroenterology. Evidence is steadily growing for the relation between dietary quality (and potential nutritional deficiencies) and mental health, and for the select use of nutrient-based supplements to address deficiencies, or as monotherapies or augmentation therapies. We present a viewpoint from an international collaboration of academics (members of the International Society for Nutritional Psychiatry Research), in which we provide a context and overview of the current evidence in this emerging field of research, and discuss the future direction. We advocate recognition of diet and nutrition as central determinants of both physical and mental health.

Lancet Psychiatry 2015; 2: 271–74

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The Melbourne Clinic (J Sarris PhD), **and Royal Melbourne Hospital** (F N Jacka PhD), **Department of Psychiatry, The University of Melbourne, Richmond, Melbourne, VIC, Australia; Centre for Human Psychopharmacology, Swinburne University of Technology, Hawthorn, VIC, Australia** (J Sarris, A Scholey PhD); **Complementary Alternative Medicine and Nutrition Research (CAMNR), Calabasas, CA, USA** (A C Logan BA); **INSERM U710 (Institut National de la Santé et de la Recherche médicale), University of Montpellier, Montpellier, France** (T N Akbaraly PhD); **Department of Epidemiology and Public Health, University College London, London, UK** (T N Akbaraly); **Orygen Youth Health Research Centre,**

Introduction

grains, lean meat, nuts, and legumes, with avoidance of

(i) Currently available drugs can show only limited benefit

(ii) Nutrition for mental health is as crucial as in other medical fields

(iii) Evidence growing for the relation between dietary quality and mental health

Adjunctive Nutraceuticals for Depression: A Systematic Review and Meta-Analyses

Jerome Sarris, Ph.D., M.H.Sc., Jenifer Murphy, Ph.D., David Mischoulon, M.D., Ph.D., George I. Papakostas, M.D., Maurizio Fava, M.D., Michael Berk, M.D., Ph.D., Chee H. Ng, M.D.

Objective: There is burgeoning interest in augmentation strategies for improving inadequate response to antidepressants. The adjunctive use of standardized pharmaceutical-grade nutrients, known as nutraceuticals, has the potential to modulate several neurochemical pathways implicated in depression. While many studies have been conducted in this area, to date no specialized systematic review (or meta-analysis) has been conducted.

Method: A systematic search of PubMed, CINAHL, Cochrane Library, and Web of Science was conducted up to December 2015 for clinical trials using adjunctive nutrients for depression. Where sufficient data were available, a random-effects model analyzed the standard mean difference between treatment and placebo in the change from baseline to endpoint, combining the effect size data. Funnel plot and heterogeneity analyses were also performed.

Results: Primarily positive results were found for replicated studies testing *S*-adenosylmethionine (SAMe), methylfolate, omega-3 (primarily EPA or ethyl-EPA), and vitamin D, with positive isolated studies for creatine, folinic acid, and an amino acid combination. Mixed results were found for zinc, folic acid, vitamin C, and tryptophan, with nonsignificant results for inositol. No major adverse effects were noted in the studies (aside from minor digestive disturbance). A meta-analysis of adjunctive omega-3 versus placebo revealed a significant and moderate to strong effect in favor of omega-3. Conversely, a meta-analysis of folic acid revealed a nonsignificant difference from placebo. Marked study heterogeneity was found in a Higgins test for both omega-3 and folic acid studies; funnel plots also revealed asymmetry (reflecting potential study bias).

Conclusions: Current evidence supports adjunctive use of SAMe, methylfolate, omega-3, and vitamin D with antidepressants to reduce depressive symptoms.

Am J Psychiatry 2016; 173:575–587; doi: 10.1176/appi.ajp.2016.15091228

PRACTICE GUIDELINE FOR THE Treatment of Patients With Major Depressive Disorder

Third Edition

- St. John's wort
- S-Adenosyl Methionine
- Omega 3 Fatty Acids
- Folates

design.

5. Complementary and alternative treatments

As defined by the National Center for Complementary and Alternative Medicine, complementary and alternative medicine is "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine." As the definitions are usually applied, "complementary" therapies are used conjunctively with conventional medicine, "alternative" therapies are used in place of conventional medicine, and "integrative" medicine makes use of all therapies appropriate to an individual patient's needs.

The use of integrative therapies is increasingly common, although training and comfort with complementary and alternative modalities vary greatly by practitioner. Many patients do not spontaneously disclose use of complementary or alternative treatments to health care professionals, so it is particularly important that direct inquiry about such treatments be part of routine health care questions. At this time, there are several modalities that have modest evidence for antidepressant efficacy and deserve further study. Some of these modalities can be recommended with enthusiasm for their general health benefits; however, patients should be informed that evidence for their antidepressant efficacy as monotherapy is limited or absent.

recommended for general

Another important co
is the potential for drug-
John's wort appears to ind
CYP 3A4, reducing the ef
antiretroviral medication
ing cyclosporine), antine
(including warfarin), ora
replacement therapy (37
have been reported with concomitant St. John's wort and oral contraceptive use (373, 375, 376), and rejection of transplanted organs has been observed when St. John's wort is taken concurrently with cyclosporin (374). The significant decreases in antiretroviral medication levels with concomitant St. John's wort use suggest that these medications will be less effective in treating HIV infection (374). Effects of St. John's wort on P-glycoprotein have also been observed, altering the pharmacokinetics and pharmacodynamics of medications such as digoxin that are transported by this route (374). Apart from affecting blood levels of nonpsychiatric medications, the safety and efficacy of the combined use of St. John's wort with other antidepressant medications is not known. The combined use of St. John's wort with MAOIs is contraindicated.

b. S-adenosyl methionine

S-adenosyl methionine is a naturally occurring molecule. In humans, it is concentrated in the liver and the brain and

serves as a methyl donor in the synthesis of biologically active compounds such as phospholipids, catecholamines,

d. Folate

Folate has been primarily assessed as a predictor of anti-

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Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 5. Complementary and Alternative Medicine Treatments

Arun V. Ravindran, MB, PhD[1], Lynda G. Balneaves, PhD[1], Guy Faulkner, PhD[2], Abigail Ortiz, MD, MSc[3], Diane McIntosh, MD[4], Rachel L. Morehouse, MD[5], Lakshmi Ravindran, MD[1], Lakshmi N. Yatham, MB, MBA (Exec)[4], Sidney H. Kennedy, MD[1], Raymond W. Lam, MD[4], Glenda M. MacQueen, MD, PhD[6], Roumen V. Milev, MD, PhD[7], Sagar V. Parikh, MD[1,8], and the CANMAT Depression Work Group[9]

Abstract

Background: The Canadian Network for Mood and Anxiety Treatments (CANMAT) conducted a revision of the 2009 guidelines by updating the evidence and recommendations. The scope of the 2016 guidelines remains the management of major depressive disorder (MDD) in adults, with a target audience of psychiatrists and other mental health professionals.

Methods: Using the question-answer format, we conducted a systematic literature search focusing on systematic reviews and meta-analyses. Evidence was graded using CANMAT-defined criteria for level of evidence. Recommendations for lines of treatment were based on the quality of evidence and clinical expert consensus. "Complementary and Alternative Medicine Treatments" is the fifth of six sections of the 2016 guidelines.

Results: Evidence-informed responses were developed for 12 questions for 2 broad categories of complementary and alternative medicine (CAM) interventions: 1) physical and meditative treatments (light therapy, sleep deprivation, exercise, yoga, and acupuncture) and 2) natural health products (St. John's wort, omega-3 fatty acids; S-adenosyl-L-methionine [SAM-e], dehydroepiandrosterone, folate, *Crocus sativus*, and others). Recommendations were based on available data on efficacy, tolerability, and safety.

Conclusions: For MDD of mild to moderate severity, exercise, light therapy, St. John's wort, omega-3 fatty acids, SAM-e, and yoga are recommended as first- or second-line treatments. Adjunctive exercise and adjunctive St. John's wort are second-line recommendations for moderate to severe MDD. Other physical treatments and natural health products have less evidence

(ii) Quali composti in quali disturbi: Depressione, Disturbi d'Ansia e del Sonno

Depressione:

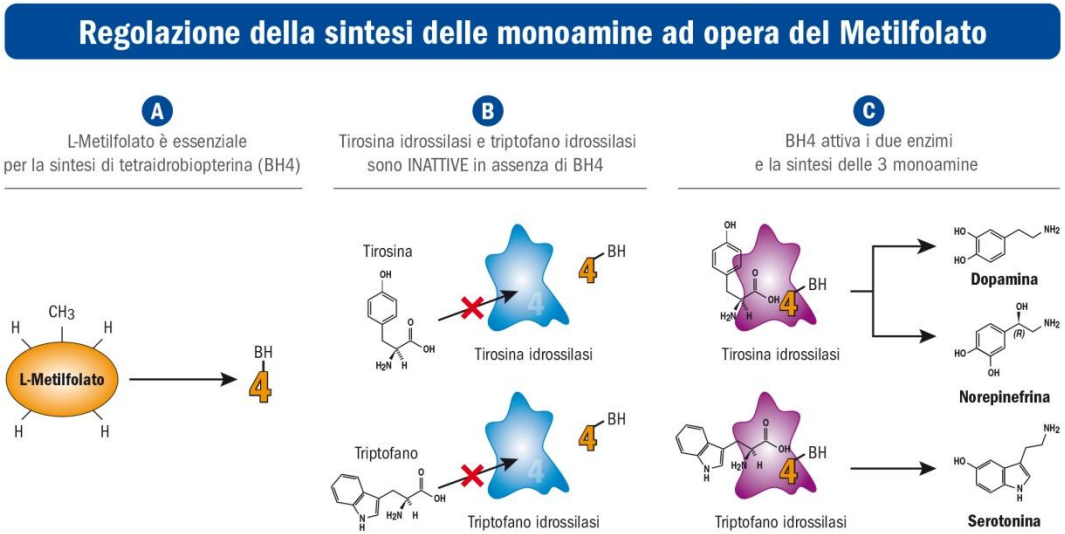
- Folati

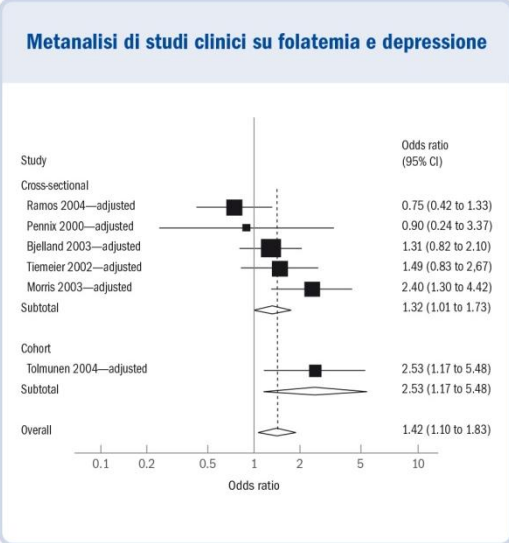
- S-AdenosilMetionina

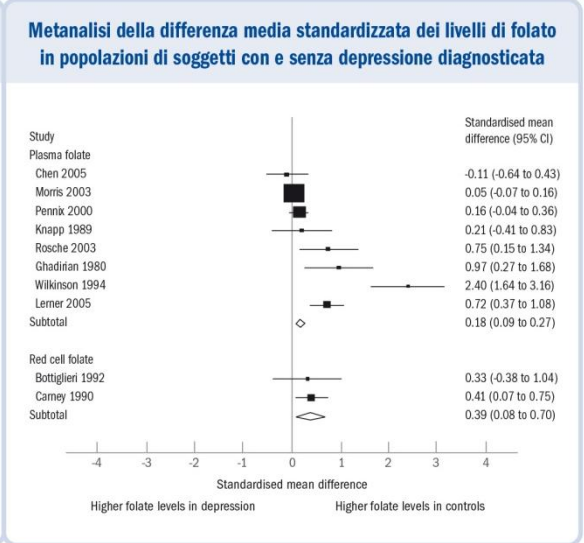
- NAC

- Omega 3 Fatty Acids
- St. John’s wort
- Vitamine D

FOLATI







Essenziali nei processi di metilazione e quindi nella sintesi di neurotrasmettitori (serotonina, dopamina e norepinefrina).
Dagli anni ’60 prime evidenze sulla **correlazione fra una deficit di folati e la depressione,** essenzialmente su due aspetti:

1. Una significativa percentuale di pazienti con diagnosi di **depressione** mostra **bassi livelli di folati**.
2. i **folati** possano essere impiegati nella **terapia di associazione all’antidepressivo** migliorando l’outcome clinico.

Questa metanalisi che ha incluso i dati di oltre 15.000 pazienti ha dimostrato una significativa relazione fra bassi livelli di folati e sviluppo di depressione (fino al 55% di rischio in più di sviluppare depressione in pazienti con bassi livelli di folati)

Stahl, J Clin Psy 2008; Gilbody et .al, J Epidemiol Comm Health 2007

ADJUNCTIVE AUGMENTATION

Authors/design/duration/main outcome measure/folate status at baseline	N	Drugs/doses (mg)	Main outcome measure (mean)	
			Baseline	Endpoint
Venkatasubramanian et al. (15) DB R AC 6 weeks HAM-D FSU	42	FLX 20 + FOL 1.5 FLX 20 + FOL 5.0	21.0 19.9	15.9 11.5 ($P = 0.02$)
Resler et al. (16) DB R PG PC 6 weeks HAM-D NF	27	FLX 20 + F FLX 20 + FOL 10.0	22.5 21.85	11.43 7.43 ($P = 0.04$)
Coppen and Bailey (17) MC DB R PG PC 10 weeks HAM-D NF	127	FLX 20 + F FLX 20 + FOL 0.5	26.6 26.8	10.7 8.1 ($P = 0.05$)
Coppen et al. (18) DB R PG 52 weeks BDI 23% (of 75) HF	75 (53 unipolar)	Li + P Li + POL 0.2	8.7 7.4	9.2 6.3 ($P = 0.02$)
Alpert et al. (19) Open-label 8 weeks HAM-D NF (SSRI-refractory patients)	22	SSRI + FOLIN 15-30	19.1	12.8 ($P < 0.01$)
Godfrey et al. (20) DB PC Adj 6 months HAM-D HF	24 (MDD patients)	Std Rx + P Std Rx + MF 15	9.0[a] 9.62[a]	11.27 8.31 ($P < 0.01$)
			% with CGI-S ≥ 2 point reduction	
Ginsberg et al. (24) SC, R, O, Retro Adj Min. 60 days CGI-S ≥ 2 points FSU	242	SSRI/SNRI SSRI/SNRI + MF 7.5-15.0	7 18.5 ($P = 0.01$)	
			% with HAM-D change ≥ 50% decrease from baseline	
Papakostas et al. (25) MC, SPC, DB, R Adj 60 days HAM-D FSU	148	SSRI + P SSRI + MF 7.5	18.8 18.3	
(SSRI-refractory patients)	75	SSRI + P SSRI + MF 15.0	14.6 32.3 ($P = 0.04$)	
Shelton et al. (26) O, TS, Adj Mean 95 days PHQ-9 FSU	595	STd Rx + MF 7.5-15.0	14.6	6.1 ($P = 0.000$)

Owen R; Drugs of Today 2013

Table 1. Characteristics of Patients With Depression Who Might Be the Best Candidates for L-Methylfolate Treatment

Documented low levels of folate and its active metabolites such as L-methylfolate

Inadequate responses to a standard antidepressant

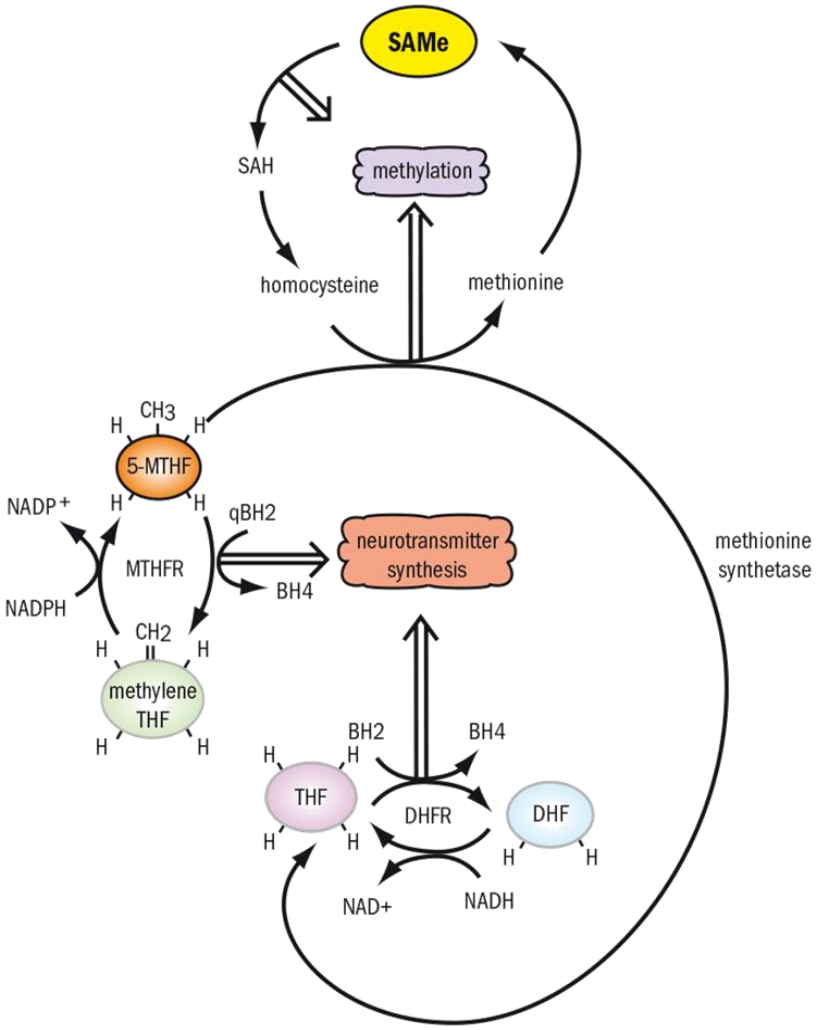
High risk for low folate levels resulting from

- Alcoholism
- Eating disorders
- Pregnancy
- Gastrointestinal disorders
- Documented low levels of MTHFR (methylene tetrahydrofolate reductase) or being from a group (Hispanic and Mediterranean populations) at high risk for decreased levels of this enzyme
- Documented high homocysteine levels, which tend to rise when folate falls
- Drugs that can interfere with folate conversion to L-methylfolate such as lamotrigine and valproate

Preference for a natural product approach with few or no side effects

Review del 2013 su 13 trials (1500 pazienti) in cui è stata valutata l'efficacia dell'acido folico o del 5-metiltetraidrofolato come terapia di add-on in pazienti MDD: in tutti è stato riscontrato un miglioramento significativo rispetto al placebo.

S-Adenosyl methionine (SAMe)



Papakostas et al. Am J Psychiatry 2010

Molecola commercializzata in Europa dagli anni ’70 per il trattamento della sintomatologia depressiva e disponibile in U.S.A. come supplemento nutrizionale dal 1999.

Il SAMe è un composto presente naturalmente nel corpo umano e rappresenta un donatore di gruppi metilici in diverse reazioni biochimiche, fra cui la metilazione delle catecolamine.

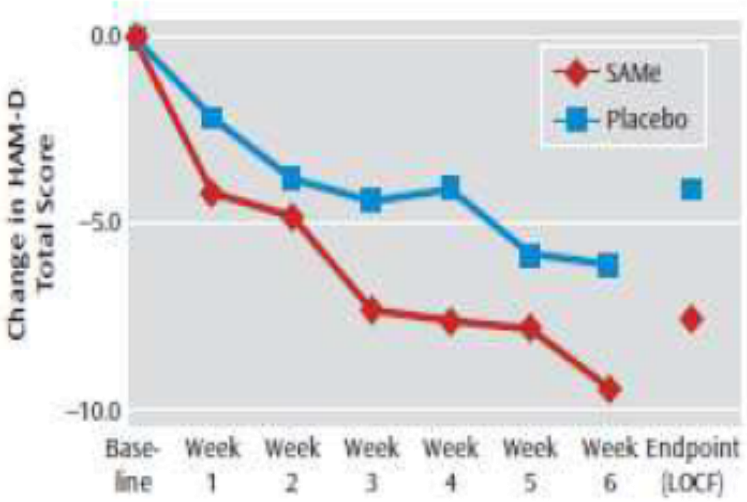
L’azione antidepressiva del SAMe potrebbe ricollegarsi a una maggior sintesi di monoamine.

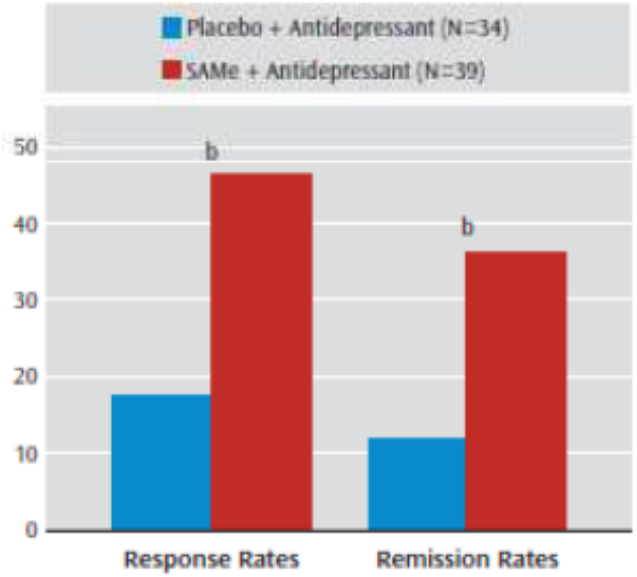
AJP American Journal of PSYCHIATRY

S-Adenosyl Methionine (SAMe) Augmentation of Serotonin Reuptake Inhibitors for Antidepressant Nonresponders With Major Depressive Disorder: A Double-Blind, Randomized Clinical Trial

George I. Papakostas, M.D.
David Mischoulon, M.D., Ph.D.
Irene Shyu, B.A.
Jonathan E. Alpert, M.D., Ph.D.
Maurizio Fava, M.D.

A 6-week RCT using adjunctive oral SAMe (target dose: 800 mg twice daily: n=73) in MDD patients unresponsive to stable SSRIs

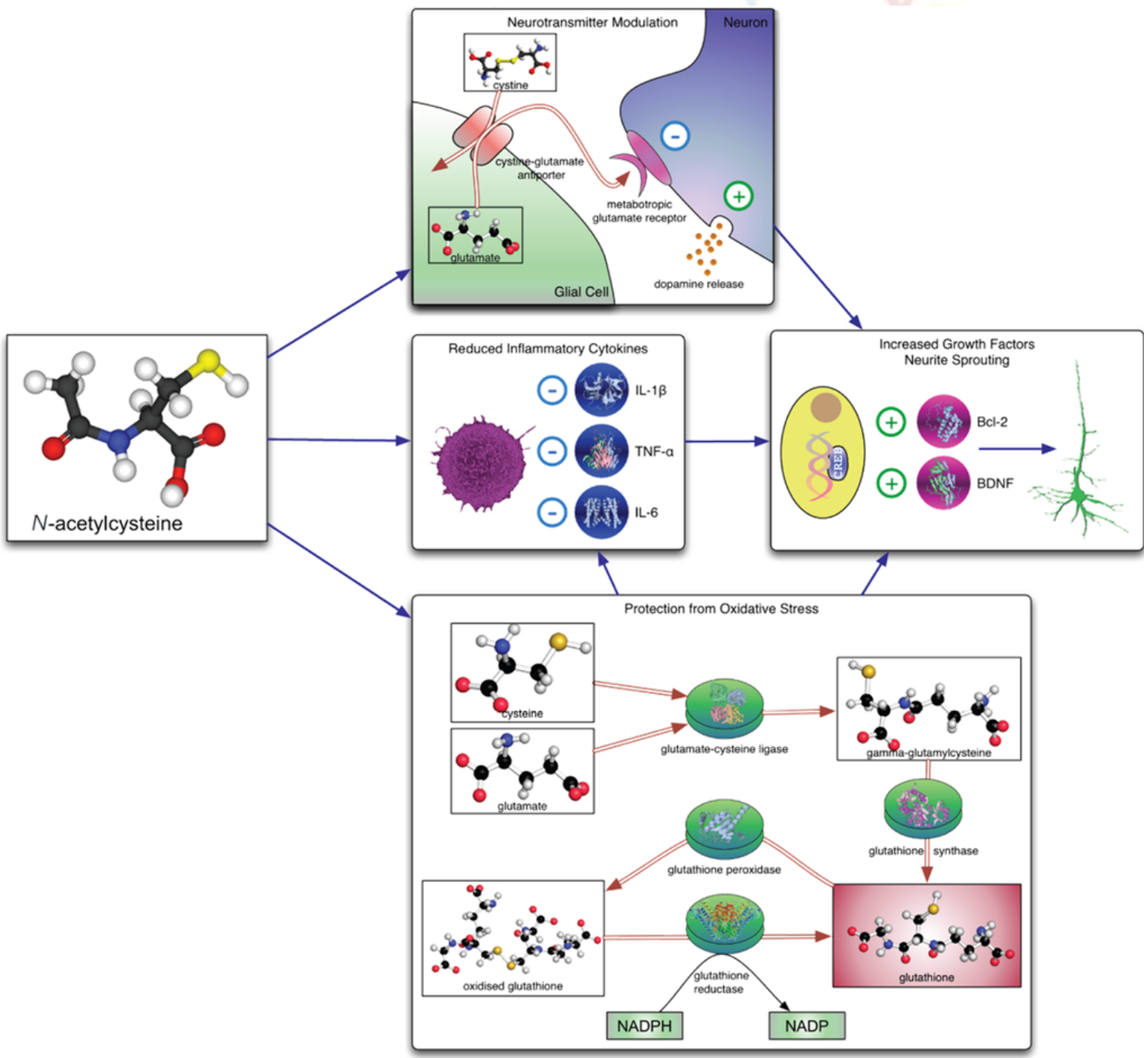




[a] Data depict last observation carried forward (LOCF) for all patients randomly assigned.
[b] Significant difference between groups ($p<0.05$, Fisher's exact test).

Response rates for SAMe-treated patients vs placebo-treated patients were 36.1% vs 17.6%, respectively, while remission rates were 25.8% vs 11.7%, respectively.

N-ACETYL CISTEINA



Il **NAC** possiede un triplice meccanismo d'azione:

- <u>attività antiossidante</u> diretta e ripristino dei livelli di glutatione, il primo antiossidante dell'organismo.
- <u>riduzione dei livelli di citochine pro-infiammatorie</u>, che risultano alterati in patologie come la depressione, il disturbo bipolare e la schizofrenia.
- <u>regolazione della trasmissione dopaminergica e glutammatergica</u> al livello del CNS, regolando il rilascio di DA e GLU dai terminali presinaptici.

ORIGINAL RESEARCH

THE JOURNAL OF CLINICAL PSYCHIATRY

The Efficacy of Adjunctive *N*-Acetylcysteine in Major Depressive Disorder: A Double-Blind, Randomized, Placebo-Controlled Trial

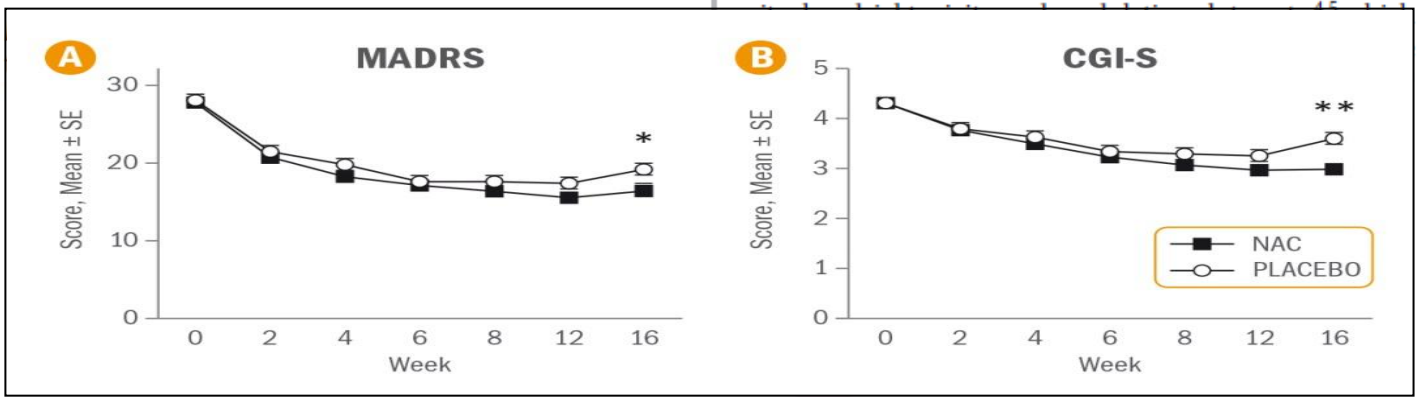
Michael Berk, MBBCh, MMed (Psych), FF(Psych)SA, PhD; Olivia M. Dean, PhD; Sue M. Cotton, PhD; Susan Jeavons, PhD; Michelle Tanious, BMedSci (Hons), BPsych (Hons); Kristy Kohlmann, BSc (Hons); Karen Hewitt, RN; Kirsteen Moss, PgDip App Psych; Christine Allwang, MD; Ian Schapkaitz, MBBCh; Jenny Robbins, RN; Heidi Cobb, BSc (Hons); Felicity Ng, MBBS; Seetal Dodd, MSc, PhD; Ashley I. Bush, MBBS, PhD; and Gin S. Malhi, MBChB, BSc (Hons), MD

ABSTRACT

Objective: Major depressive disorder (MDD) is one of the most common psychiatric disorders, conferring considerable individual, family, and community burden. To date, treatments for MDD have been derived from the monoamine hypothesis, and there is a paucity of emerging antidepressants, especially with novel mechanisms of action and treatment targets. *N*-acetylcysteine (NAC) is a redox-active glutathione precursor that decreases inflammatory cytokines, modulates glutamate, promotes neurogenesis, and decreases apoptosis, all of which contribute to the neurobiology of depression.

Method: Participants with a current episode of MDD diagnosed according to *DSM-IV-TR* criteria (N = 252) were treated with NAC or placebo in addition to treatment as usual for 12 weeks and were followed to 16 weeks. Data were collected between 2007 and 2011.

Considerable attention has been paid recently to the weak pipeline of emerging agents in psychiatry, and in particular, the paucity of truly novel antidepressant agents.[1] New insights into the putative biology of depression have indicated alternative mechanisms of action for the development of novel antidepressants, including inflammation and oxidative stress. Glutathione, a tripeptide consisting of glutamate, glycine, and cysteine, is the dominant free radical scavenger within the brain that buffers reactive oxidative species. *N*-acetylcysteine can reliably enhance the synthesis of glutathione by increasing the availability of cysteine, the rate-limiting synthetic step.[2,3] *N*-acetylcysteine also has other actions germane to the known pathophysiology of depression, such as enhancing neurogenesis, blocking apoptosis, reducing inflammation, protecting against



Journal of Affective Disorders 135 (2011) 389–394

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Journal of Affective Disorders

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

Brief report

The efficacy of N-acetylcysteine as an adjunctive treatment in bipolar depression: An open label trial☆

Michael Berk [a,b,c,h,*], Olivia Dean [a,c,h], Sue M. Cotton [b], Clarissa S. Gama [d], Flavio Kapczinski [d], Brisa S. Fernandes [d], Kristy Kohlmann [h], Susan Jeavons [a,e], Karen Hewitt [h], Christine Allwang [f,g,i], Heidi Cobb [f,g], Ashley I. Bush [c], Ian Schapkaitz [h], Seetal Dodd [a,h], Gin S. Malhi [f,g]

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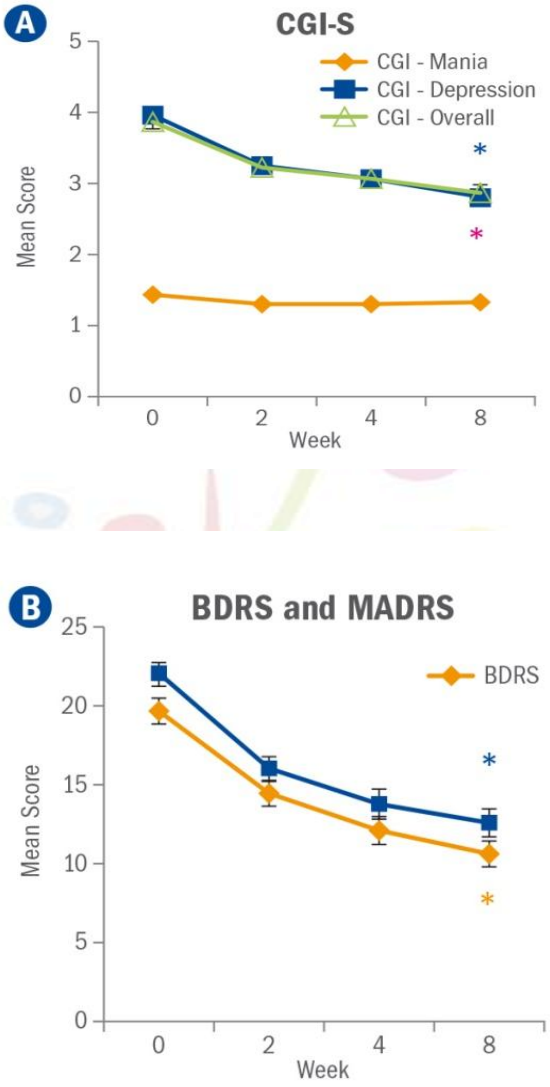
ABSTRACT

Background: Evidence is accumulating to support the presence of redox dysregulation in a number of psychiatric disorders, including bipolar disorder. This dysregulation may be amenable to therapeutic intervention. Glutathione is the predominant non-enzymatic intracellular free radical scavenger in the brain, and the most generic of all endogenous antioxidants in terms of action. N-acetylcysteine (NAC) is a glutathione precursor that effectively replenishes brain glutathione. Given the failure of almost all modern trials of antidepressants in bipolar disorder to demonstrate efficacy, and the limited efficacy of mood stabilisers in the depressive phase of the disorder, this is a major unmet need.

Method: This study reports data on the treatment of 149 individuals with moderate depression during the 2 month open label phase of a randomised placebo controlled clinical trial of the efficacy of 1 g BID of NAC that examined the use of NAC as a maintenance treatment for bipolar disorder.

Results: In this trial, the estimated mean baseline Bipolar Depression Rating Scale (BDRS) score was 19.7 ($SE=0.8$), and the mean BDRS score at the end of the 8 week open label treatment phase was 11.1 ($SE=0.8$). This reduction was statistically significant ($p<0.001$). Improvements in functioning and quality of life were similarly evident.

Conclusion: These open label data demonstrate a robust decrement in depression scores with NAC treatment. Large placebo controlled trials of acute bipolar depression are warranted.



Disturbi del Sonno/d'Ansia:

- L-Teanina
- Crisina (Passiflora)
- Baicaleina (Scutellaria)
- Melatonina

L-TEANINA

(-glutamiletilamide) amminoacido puro estratto dal tè verde con capacità d'indurre una sensazione di rilassamento.

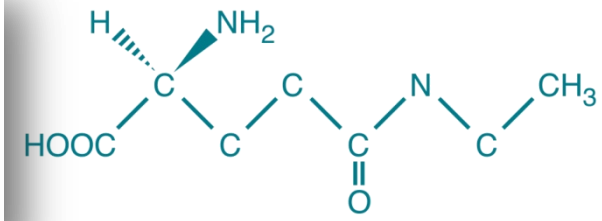


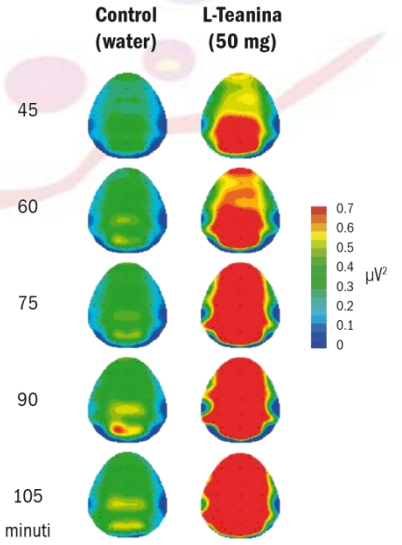
Table 1 Effect of L-Theanine on brain neurotransmitter levels

	Neurotransmitter							
Brain region	Glutamate	Glycine	GABA	Serotonin	Dopamine	Catecholamines	Aspartate	BDNF
General	↓[10] ↔[19*]	↑[12,18]	↑[12,18*]	↓[10]	↑[8]	↓[7]	↓[8,18]	↑[14,15,22]
Midbrain/striatum	↔[8]	↑[8]	ND	↑[14,17]	↑[8,14,17] ↓[23§]	ND	↓[8]	ND
Hippocampus	↔[19*]	ND	↔[19*]	↑[14,17]	↑[14,17]	↑[24]	ND	↑[8,15,18]
Hypothamalus	ND	ND	ND	↑[14,17] ↔[12]	↑[14,17] ↔[12]	ND	ND	ND
Cerebrum/cortex	↔[19*]	ND	↑[7]	↓[17,20,25*] ↔[12]	↔[12]	↑[24]	ND	ND
Cultured neurons	↓[10]	ND	ND	ND	ND	ND	ND	ND

Note: Parentheses refer to reference number; ↔= no change; ND = not done; *chronic administration; §nicotine-treated.

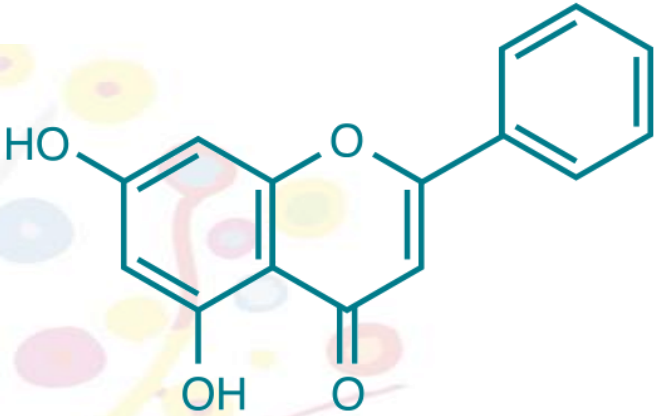
La L-Teanina agisce come neurotrasmettitore a livello cerebrale, stimolando la produzione delle onde alfa cerebrali

In un recente studio clinico si è valutato l'EEG in soggetti sani alla baseline e 45, 60, 75, 90 e 105 minuti dopo somministrazione orale di L-Teanina 50mg (n=16) o placebo (n=19). I participanti erano in condizioni di riposo e con occhi chiusi durante la registrazione. E' stato rilevato un considerevole aumento dell'attività delle onde alfa-1 nel gruppo L-Teanina rispetto al placebo ($p<0.05$).



CRISINA

Principale flavonoide contenuto nell'estratto di Passiflora Incarnata, fitoterapico ad attività ansiolitica/proipnotica più comune e meglio studiato.
Il suo meccanismo d'azione è legato alla modulazione del sistema gabaergico (azione agonista sul recettore GABA-A).



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Modulation of the γ-Aminobutyric Acid (GABA) System by *Passiflora incarnata* L.

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***Passiflora incarnata* L. (Passifloraceae) is important in herbal medicine for treating anxiety or nervousness, Generalized Anxiety Disorder (GAD), symptoms of opiate withdrawal, insomnia, neuralgia, convulsion, spasmodic asthma, ADHD, palpitations, cardiac rhythm abnormalities, hypertension, sexual dysfunction and menopause. However, the mechanism of action is still under discussion. Despite gaps in our understanding of neurophysiological processes, it is increasingly being recognized that dysfunction of the GABA system is implicated in many neuropsychiatric conditions, including anxiety and depressive disorders. Therefore, the *in vitro* effects of a dry extract of *Passiflora incarnata* (sole active ingredient in Pascoflair® 425 mg) on the GABA system were investigated. The extract inhibited [^{3}H]-GABA uptake into rat cortical synaptosomes but had no effect on GABA release and GABA transaminase activity. *Passiflora incarnata* inhibited concentration dependently the binding of [^{3}H]- SR95531 to $GABA_A$-receptors and of [^{3}H]-CGP 54626 to $GABA_B$-receptors. Using the [^{35}S]-GTPγS binding assay *Passiflora* could be classified as an antagonist of the $GABA_B$ receptor. In contrast, the ethanol- and the benzodiazepine-site of the $GABA_A$-receptor were not affected by this extract.**

In conclusion, the first evidence was shown that numerous pharmacological effects of *Passiflora incarnata* are mediated via modulation of the GABA system including affinity to $GABA_A$ and $GABA_B$ receptors, and effects on GABA uptake.

Passiflora for anxiety disorder (Review)

Miyasaka LS, Atallah ÁN, Soares B

THE COCHRANE COLLABORATION®

ABSTRACT

Background

Anxiety is a very common mental health problem in the general population and in the primary care setting. Herbal medicines are popularly used worldwide and could be an option for treating anxiety if shown to be effective and safe. Passiflora (passionflower extract) is one of these compounds.

Objectives

To investigate the effectiveness and safety of passiflora for treating any anxiety disorder.

Search methods

The following sources were used: electronic databases: Cochrane Collaboration Depression, Anxiety and Neurosis Cochrane Controlled Trials Register (CCDANCTR-Studies), Medline and Lilacs; Cross-checking references; contact with authors of included studies and manufacturers of passiflora.

Selection criteria

Relevant randomised and quasi-randomised controlled trials of passiflora using any dose, regime, or method of administration for people with any primary diagnosis of general anxiety disorder, anxiety neurosis, chronic anxiety status or any other mental health disorder in which anxiety is a core symptom (panic disorder, obsessive compulsive disorder, social phobia, agoraphobia, other types of phobia, postraumatic stress disorder). Effectiveness was measured using clinical outcome measures such as Hamilton Anxiety Scale (HAM-A) and other scales for anxiety symptoms.

Data collection and analysis

Two reviewers independently selected the trials found through the search strategy, extracted data, performed the trial quality analyses and entered data. Where any disagreements occured, the third reviewer was consulted. Methodological quality of the trials included in this review was assessed using the criteria described in the Cochrane Handbook. For dichotomous outcomes, relative risk with 95% confidence intervals (CI) were calculated, and for continuous outcomes, weighted mean difference with 95%CI was used.

Main results

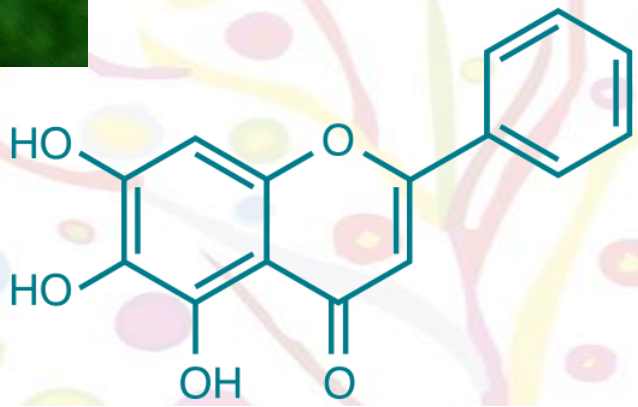
Two studies, with a total of 198 participants, were eligible for inclusion in this review. Based on one study, a lack of difference in the efficacy of benzodiazepines and passiflora was indicated. Dropout rates were similar between the two interventions. Although the findings from one study suggested an improvement in job performance in favour of passiflora (post-hoc outcome) and one study showed a lower rate of drowsiness as a side effect with passiflora as compared with mexazolam, neither of these findings reached statistical significance.

Authors' conclusions

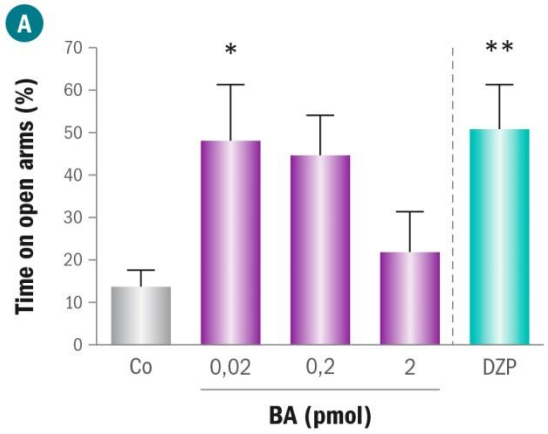
RCTs examining the effectiveness of passiflora for anxiety are too few in number to permit any conclusions to be drawn. RCTs with larger samples that compare the effectiveness of passiflora with placebo and other types of medication, including antidepressants, are needed.

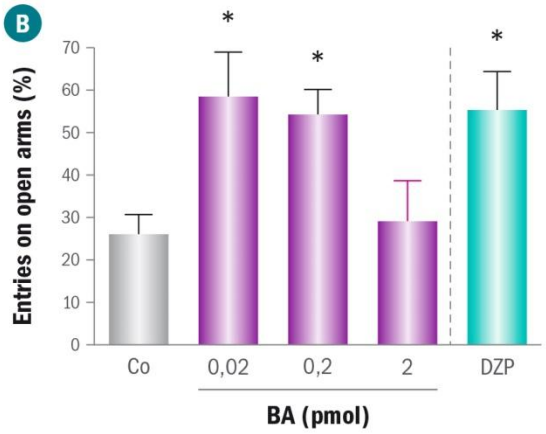
La review **Cochrane** ha preso in considerazione 2 studi randomizzati per un totale di 198 partecipanti (Akhondzadeh 2001 n=36; Mori 1993 n=162) in cui la passiflora è stata valutata verso benzodiazepine.
Lo studio di Mori et. al ha mostrato un miglioramento simile, da moderato ad importante, passiflora vs mexazolam (37% vs 44%) mentre il lavoro di Akhondzadeh, che ha valutato passiflora vs oxazepam non ha mostrato differenze in termini di efficacia e, sebbene l'oxazepam avesse un più rapido inizio d'azione, la passiflora ha mostrato un minor impatto sulle performance lavorative dei pazienti. Complessivamente si è verificato un minor rischio di sedazione rispetto a quanto riscontrato con le benzodiazepine e non sono state individuate particolari problematiche di sicurezza per questo prodotto.

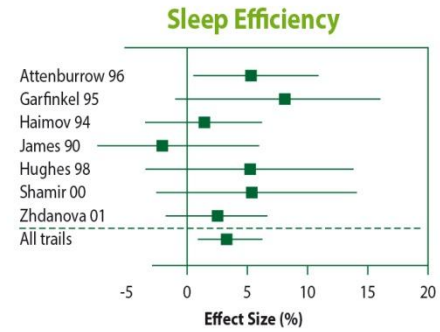
BAICALEINA

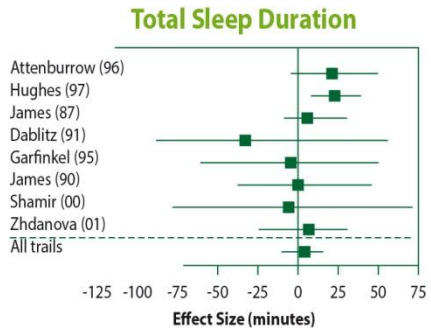


La Baicaleina, flavone dell'estratto di Scutellaria, ha un effetto ansiolitico dovuto all' attività sul recettore $GABA_A$ ma con interazione in un sito di legame diverso rispetto a quello delle benzodiazepine.
Questo lavoro mostra come in un modello sperimentale di ansia (elevated plus maze), la scutellaria abbia un effetto ansiolitico paragonabile al diazepam ad un dosaggio molto basso, effetto in questo caso non completamente antagonizzato dalla somministrazione di flumazenil.

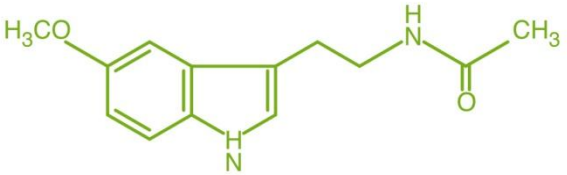








Melatonina



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PLOS ONE

Meta-Analysis: Melatonin for the Treatment of Primary Sleep Disorders

Eduardo Ferracioli-Oda[1*¤], Ahmad Qawasmi[2,3], Michael H. Bloch[2,4]

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Abstract

Study Objectives: To investigate the efficacy of melatonin compared to placebo in improving sleep parameters in patients with primary sleep disorders.

Design: PubMed was searched for randomized, placebo-controlled trials examining the effects of melatonin for the treatment of primary sleep disorders. Primary outcomes examined were improvement in sleep latency, sleep quality and total sleep time. Meta-regression was performed to examine the influence of dose and duration of melatonin on reported efficacy.

Participants: Adults and children diagnosed with primary sleep disorders.

Interventions: Melatonin compared to placebo.

Results: Nineteen studies involving 1683 subjects were included in this meta-analysis. Melatonin demonstrated significant efficacy in reducing sleep latency (weighted mean difference (WMD) = 7.06 minutes [95% CI 4.37 to 9.75], Z = 5.15, p<0.001) and increasing total sleep time (WMD = 8.25 minutes [95% CI 1.74 to 14.75], Z = 2.48, p = 0.013). Trials with longer duration and using higher doses of melatonin demonstrated greater effects on decreasing sleep latency and increasing total sleep time. Overall sleep quality was significantly improved in subjects taking melatonin (standardized mean difference = 0.22 [95% CI: 0.12 to 0.32], Z = 4.52, p<0.001) compared to placebo. No significant effects of trial duration and melatonin dose were observed on sleep quality.

Conclusion: This meta-analysis demonstrates that melatonin decreases sleep onset latency, increases total sleep time and improves overall sleep quality. The effects of melatonin on sleep are modest but do not appear to dissipate with continued melatonin use. Although the absolute benefit of melatonin compared to placebo is smaller than other pharmacological treatments for insomnia, melatonin may have a role in the treatment of insomnia given its relatively benign side-effect profile compared to these agents.

Ormone naturalmente prodotto dalla ghiandola pineale, la melatonina ha attività ipnoinducente e regolatrice del ritmo sonno-veglia dimostrata in decine di trial clinici e metanalisi. E' inoltre nota l'assenza di effetti negativi sulle performance psicomotorie e cognitive al mattino.

Conclusioni

- Un corretto bilancio nutrizionale riveste un ruolo centrale per la salute mentale così come per altri ambiti della medicina.

- L'utilizzo della nutraceutica nel trattamento di alcuni disturbi psichiatrici (Disturbi Depressivi, Disturbi del Sonno e d'Ansia) e in specifici contesti (sintomi prodromici, strategie d'augmentation, sintomi residui) è supportato da una serie di recenti revisioni sistematiche, meta-analisi e Linee Guida.

- Allo stato attuale i composti di nutraceutica con maggiori evidenze nel trattamento dei Disturbi dell'Umore sono i Folati, la S-AdenosilMetionina, NAC, Omega 3 Fatty Acids, Vitamina D, mentre per i Disturbi del Sonno e d'Ansia sono la Teanina, la Cresina, la Baicaleina e la Melatonina.