Nutraceuticals στις Συναισθηματικές Διαταραχές

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Ψυχίατρος - Ψυχοθεραπευτής

22 Απριλίου 2017
Ιωάννινα

ΔΗΛΩΣΗ ΣΥΓΚΡΟΥΣΗΣ ΣΥΜΦΕΡΟΝΤΩΝ

ΤΑΚΤΙΚΕΣ ΑΠΟΔΟΧΕΣ: Ιδιωτικό Ιατρείο (Αθήνα), Υ.ΕΘ.Α

ΟΜΙΛΙΕΣ: Servier, Janssen, Specifar, Brain

ΜΕΛΕΤΕΣ: Lundbeck, Bristol

ΕΚΠΑΙΔΕΥΣΗ: Servier, Janssen, Pfizer, Lundbeck

Ορισμός

- Ο όρος “nutraceutical” προέρχεται από τον συνδυασμό 2 λέξεων:

  “nutrition” +“pharmaceutical”

- Ο όρος επινοήθηκε το 1989 από τον Stephen De Felice, ιδρυτής και πρόεδρος του “Foundation for Innovation in Medicine”

Nutraceuticals

- «…κάθε ουσία ή συστατικό αυτής όπου εκτός της διατροφικής της αξίας παρέχει, επιστημονικά τεκμηριωμένα, οφέλη στην υγεία, τόσο στην πρόληψη και θεραπεία παθήσεων και διαταραχών όσο και στην εν γένει βελτίωση της υγείας των ανθρώπων…»

- «…φάρμακο σας να γίνει η τροφή σας και η τροφή σας ας γίνει φάρμακο σας…»

(ΙΠΠΟΚΡΑΤΗΣ)

Hamid N.New Concepts in Nutraceuticals as Alternative for Pharmaceuticals
Int J Prev Med. 2014 Dec; 5(12): 1487–1499.
Kalra EK. Nutraceutical – Definition and introduction. AAPS Pharm Sci. 2003;5:E25
Zeisel SH. Regulation of "nutraceuticals" Science. 1999;285:1853–5

Υπάρχει ανάγκη για μια νέα προσέγγιση;

Αποτελεσματικότητα

- Καθυστέρηση στην έναρξη δράσης
- 1/3 των ασθενών δεν απαντούν, 2/3 των ασθενών δεν επιτυγχάνουν ύφεση
- Η μέση αποτελεσματικότητα όλων των θεραπειών δεν παρουσιάζει διαφοροποίηση

Προφίλ ανοχής και ασφάλειας

- Επιδείνωση άγχους- διαταραχών ύπνου και γαστρεντερικές Α.Ε στην έναρξη της φαρμακευτικής αγωγής
- Σεξουαλική δυσλειτουργία, καταστολή, συναισθηματική άμβλυνση, συμπτώματα απόσυρσης

Συμμόρφωση

- 42% διακόπτουν τον 1ο μήνα και 70% στο πρώτο 3μηνο
- 45% δεν λαμβάνουν τη φ.α. όπως έχει συσταθεί

Moncrieff & Kirsch BMJ 2005

Olfson et al Lancet 2006, Sawada et al 2009

Θεραπευτικοί στόχοι στην κατάθλιψη

MDD Treatment Objectives

1970s	1990s
Response	**Remission**
Many symptoms remain • Reduction of symptoms by ≥50% using scales such as MADRS or HAM-D	**Some symptoms may persist** • Definition varies between studies but commonly defined as MADRS score of ≤10 or HAM-D17 score of ≤7

MADRS = Montgomery-Åsberg Depression Rating Scale;
HAM-D = Hamilton Depression Rating Scale;
HAM-D17 = Hamilton Depression Rating Scale 17-item version

Medscape EDUCATION

Θεραπευτικοί στόχοι στην κατάθλιψη

MDD Treatment Objectives (cont)

1970s	1990s	2010
Response **Many symptoms remain** • Reduction of symptoms by ≥50% using scales such as MADRS or HAM-D	**Remission** **Some symptoms may persist** • Definition varies between studies but commonly defined as MADRS score of ≤10 or HAM-D17 score of ≤7	**Full Functional Recovery** **Symptoms may still be present or are absent** • Not officially defined; measures should include clinician rating, self-report, and performance testing to assess both symptoms and functioning

Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2013: 127 (Suppl. 443) : 6–23

DOI: 10.1111/acps.12122

ACTA PSYCHIATRICA SCANDINAVICA

Clinical overview

Pharmacological management of unipolar depression

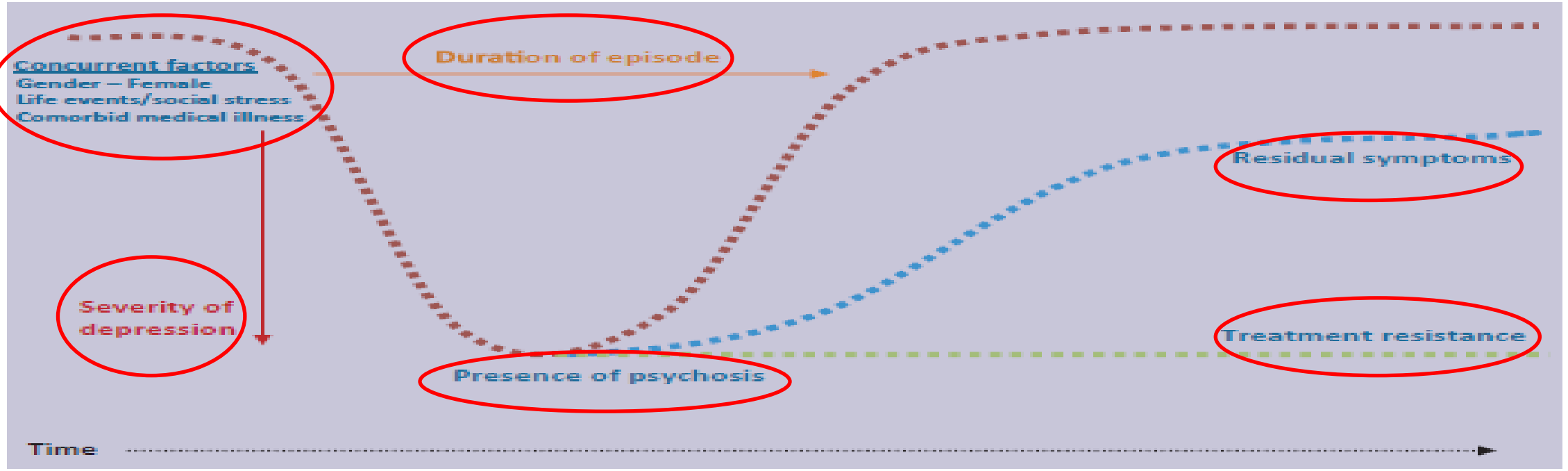
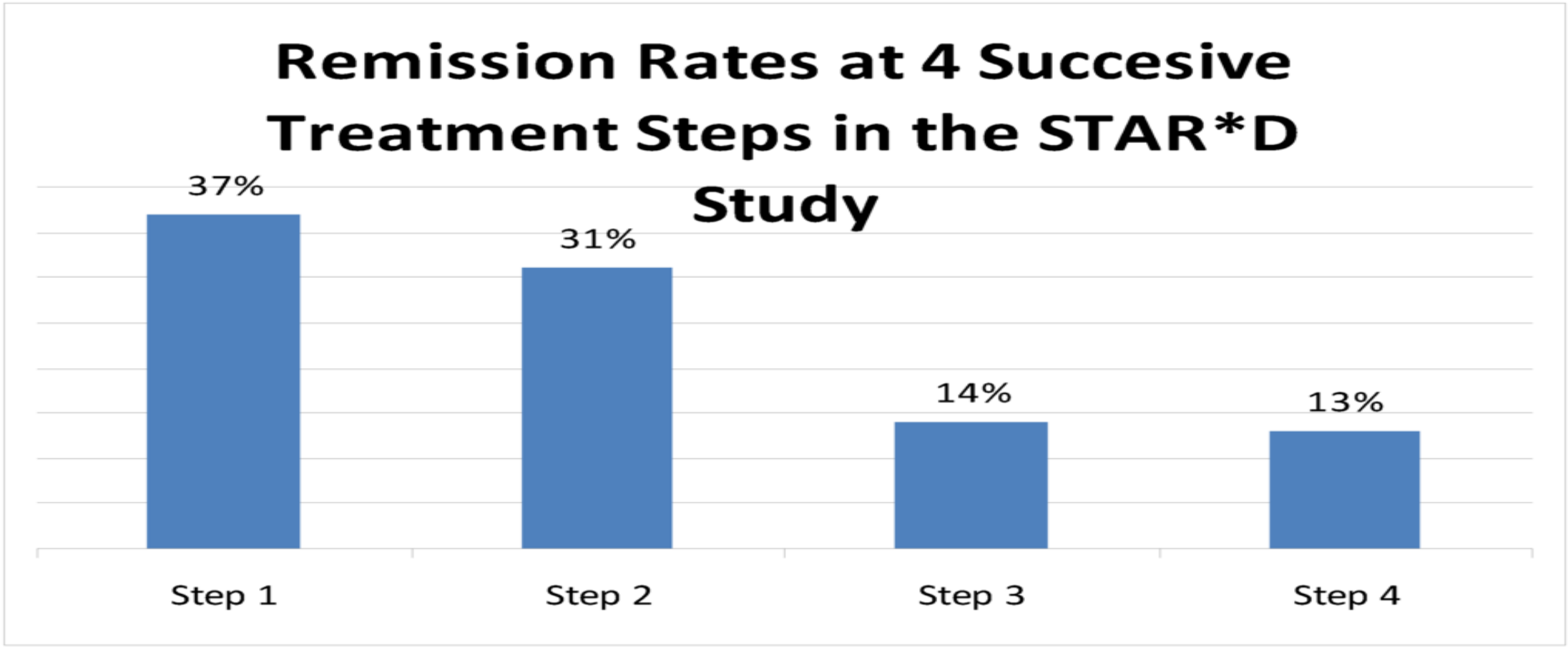


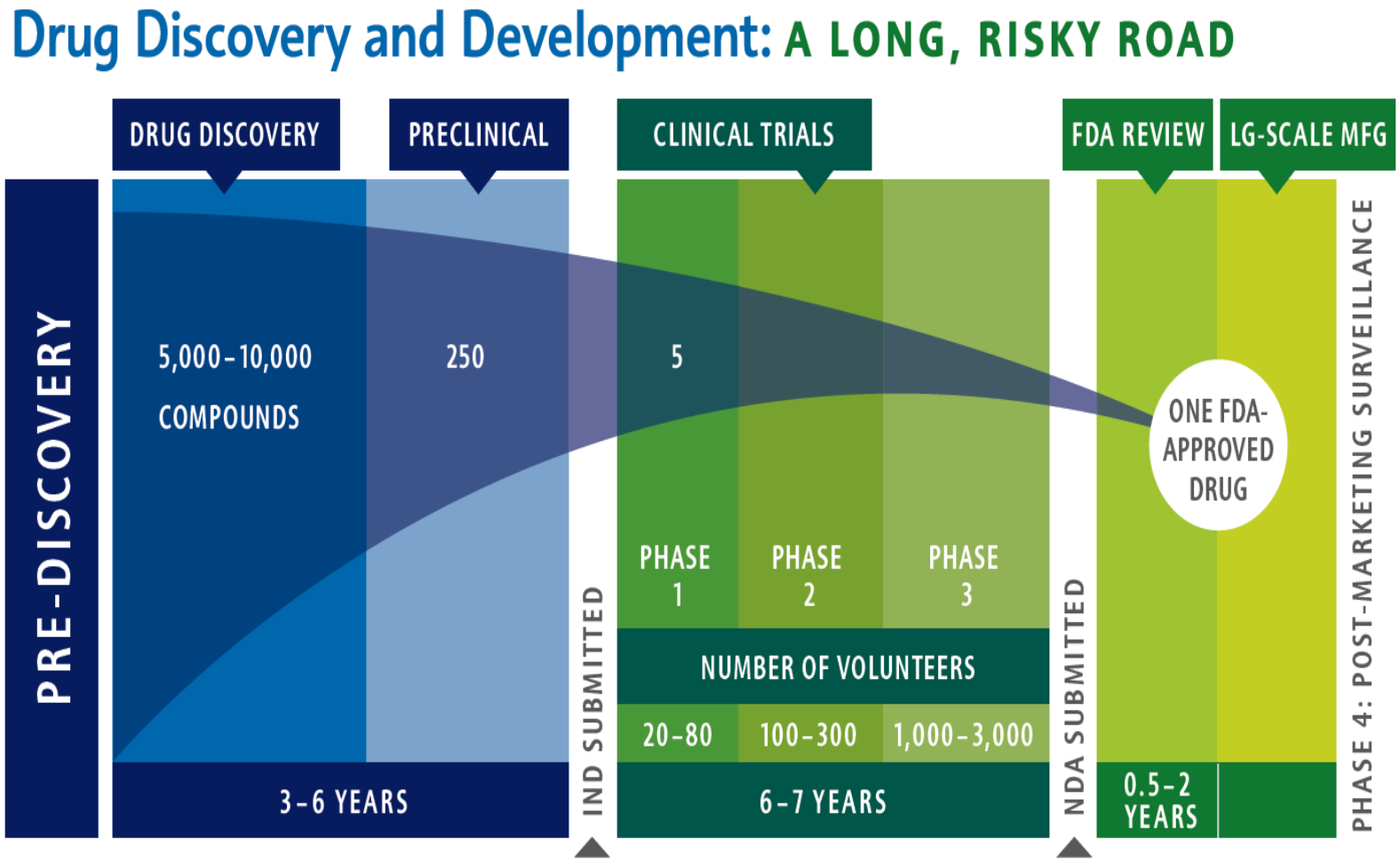
Fig. 7. Factors increasing the risk of acute relapse in depression. Concurrent factors should be taken into consideration when choosing treatment options. Note. Specific factors that increase the risk of relapse are labelled at the point of where they are likely to impact treatment.

Malhi GS, Hitching R, Berk M, Boyce P, Porter R, Fritz K. Pharmacological management of unipolar depression.

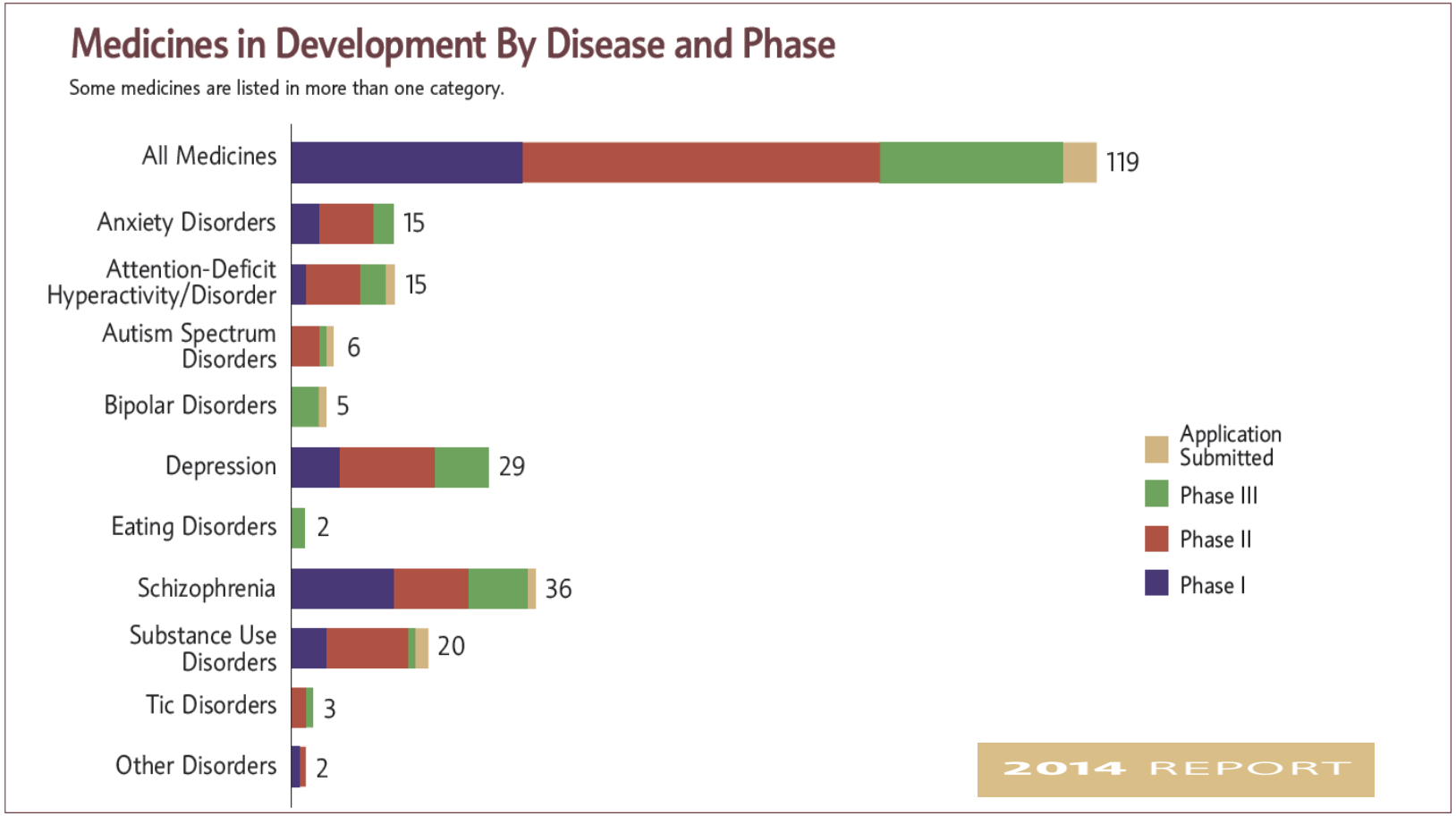
Η απογοήτευση της μελέτης STAR*D…



Η ανακάλυψη και ανάπτυξη ενός φαρμάκου...

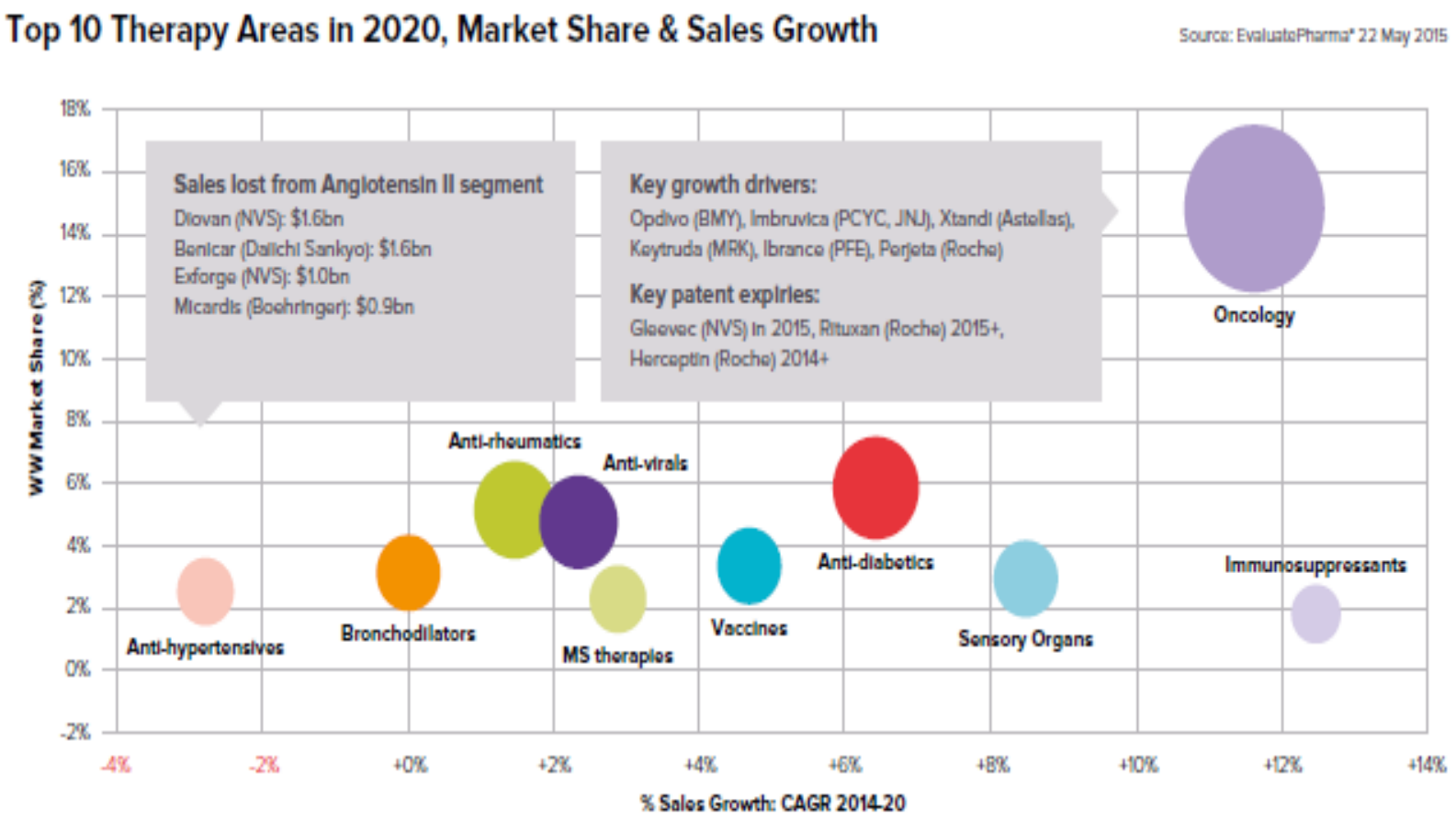


Το μέλλον της ψυχιατρικής…



PRESENTED BY AMERICA'S BIOPHARMACEUTICAL RESEARCH COMPANIES

Το κοντινό 2020...



Nutraceuticals στις Συναισθηματικές Διαταραχές

Παθοφυσιολογία της κατάθλιψης

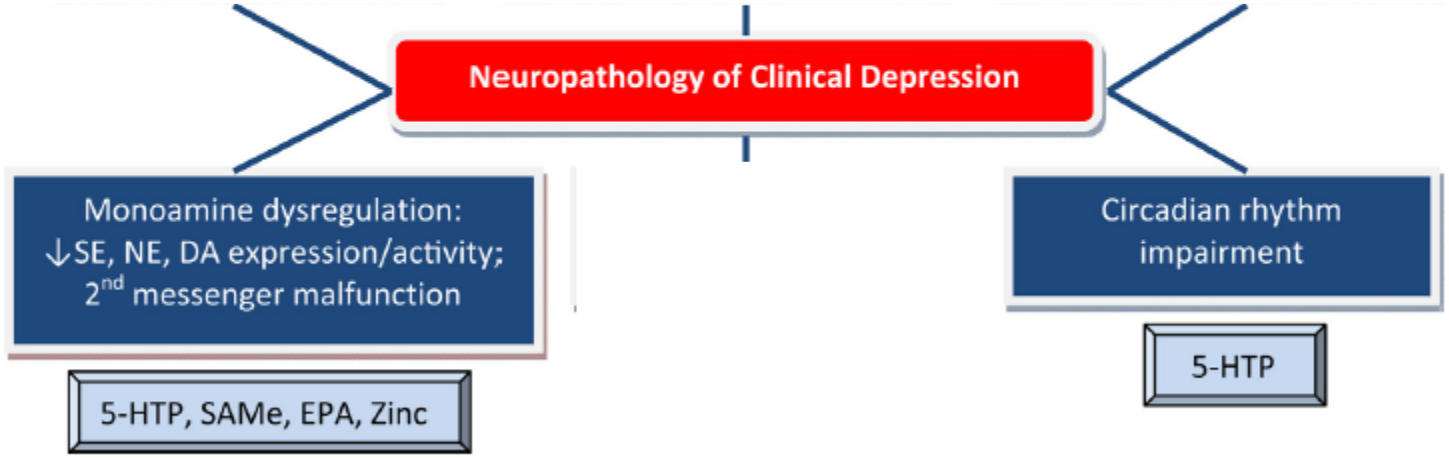


Fig. 1. Pathophysiology of depression and the nutraceuticals modulating these neurochemical pathways.

Sarris et all, An adjunctive antidepressant nutraceutical combination in treating major depression: Study protocol, and clinical considerations - Advances in Integrative Medicine 2 (2015) 49–55

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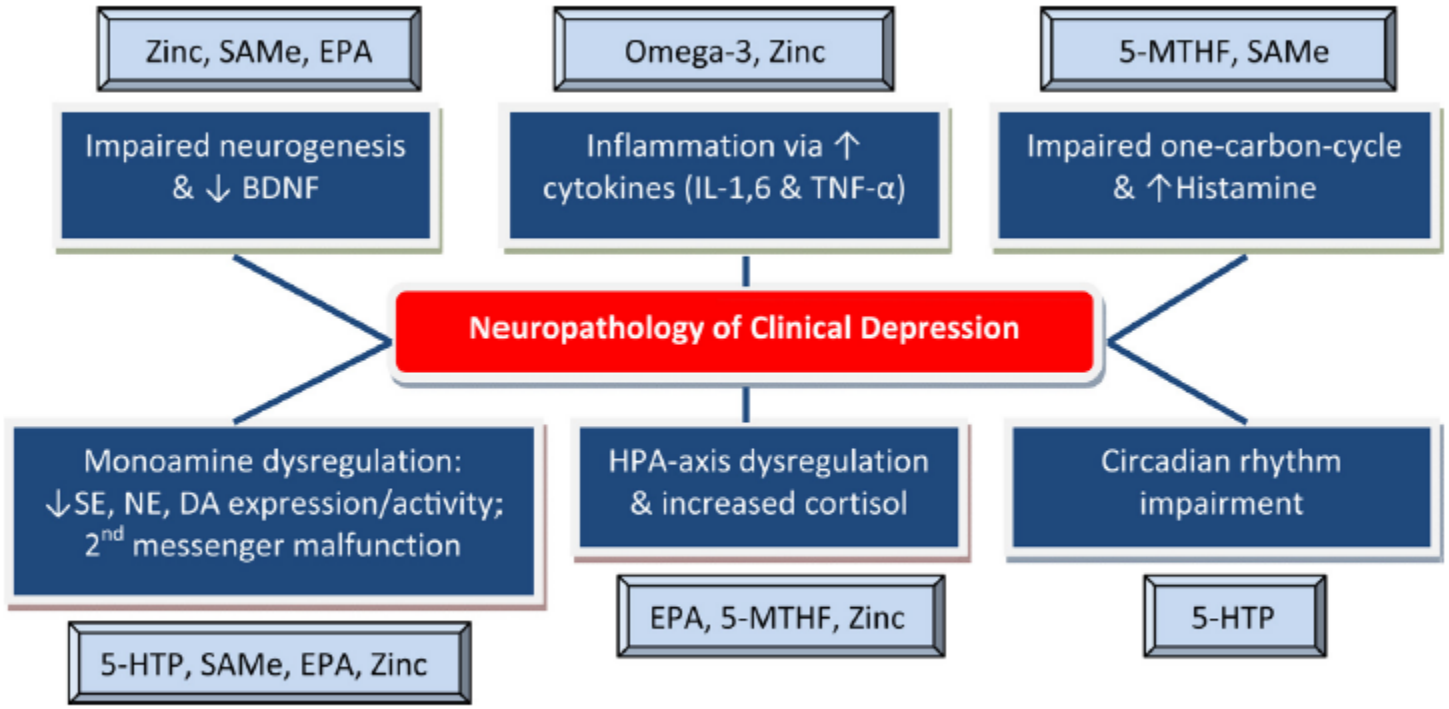

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Αντικαταθλιπτική δράση

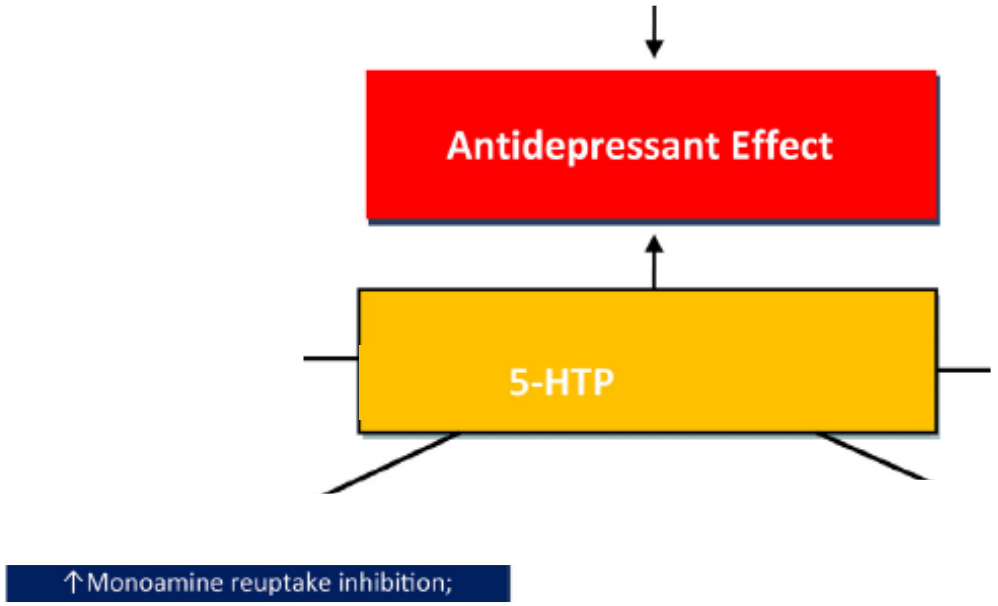

Fig. 2. SAMe and other key nutraceuticals with antidepressant activity.

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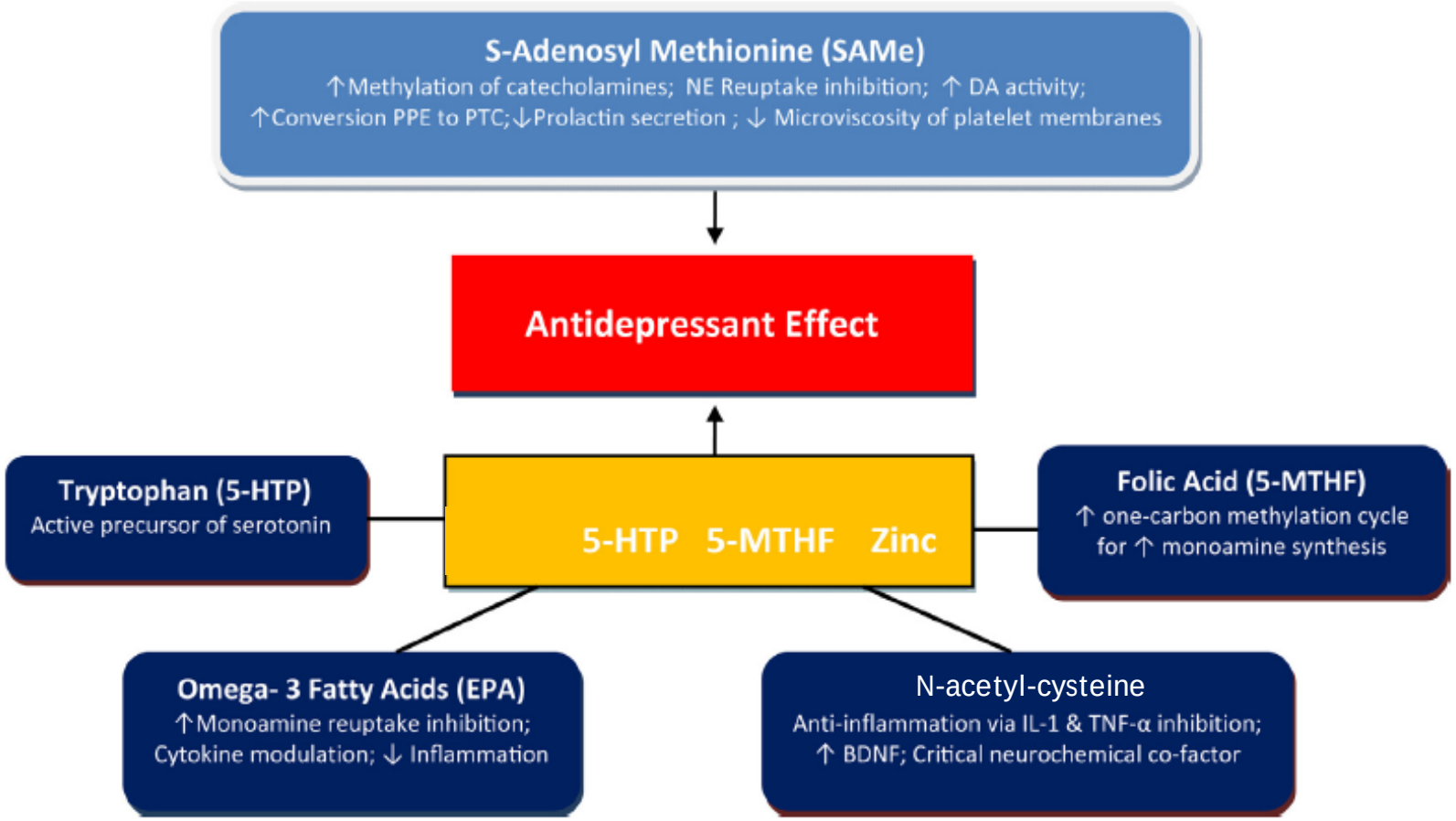

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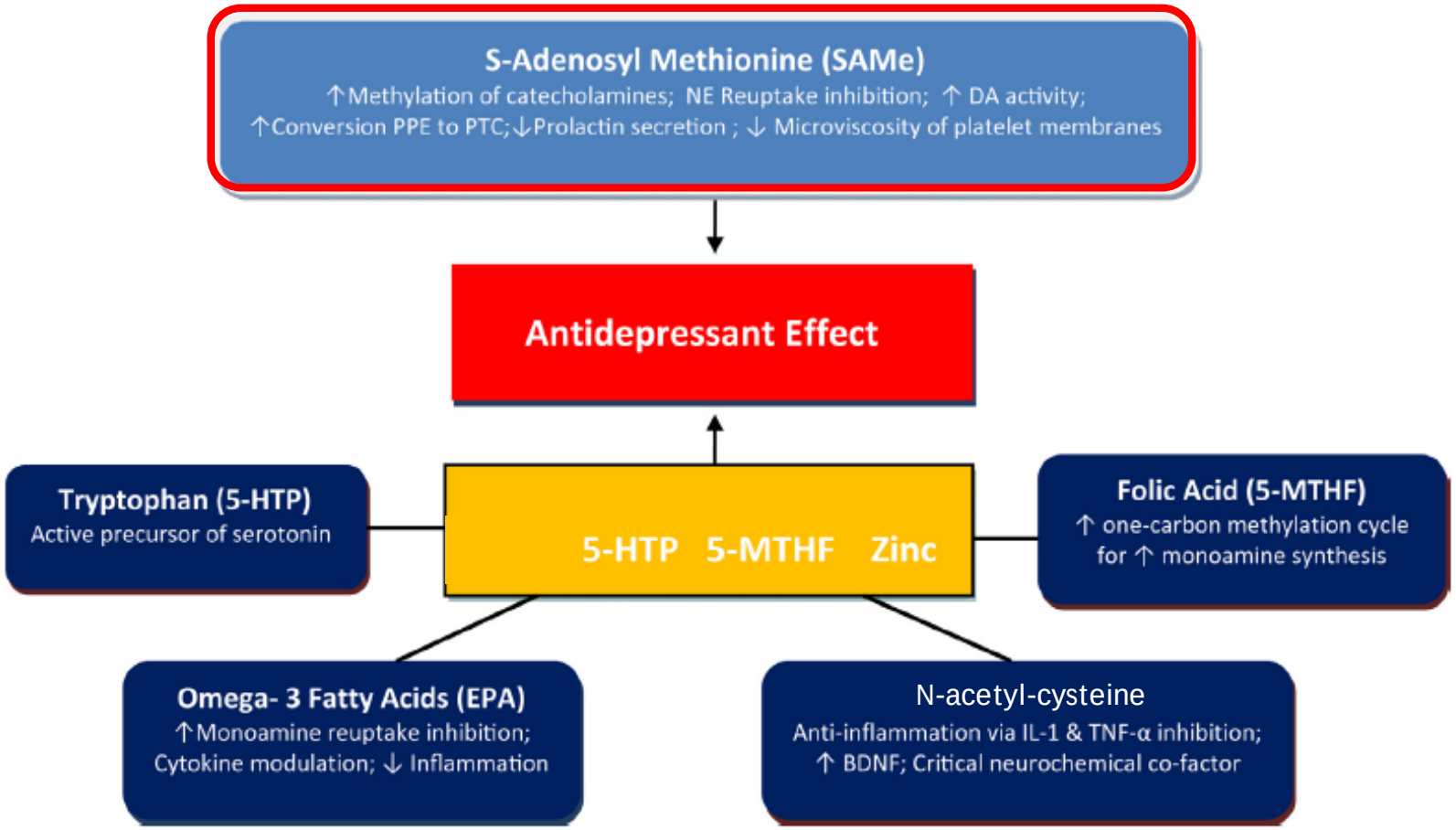

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S-αδενόσυλ-L-μεθειονίνη (SAMe)

- Συνθετική μορφή αμινοξέως, παράγωγο μεθειονίνης
  λειτουργεί ως δότης μεθυλίου,
  εμπλέκεται στη μεθυλίωση περισσότερων από 100 αντιδράσεων

- Σύνθεση DNA - RNA, πρωτεϊνών, φωσφολιπιδίων, νευροδιαβιβαστών, κυστεΐνης, γλουταθειόνης

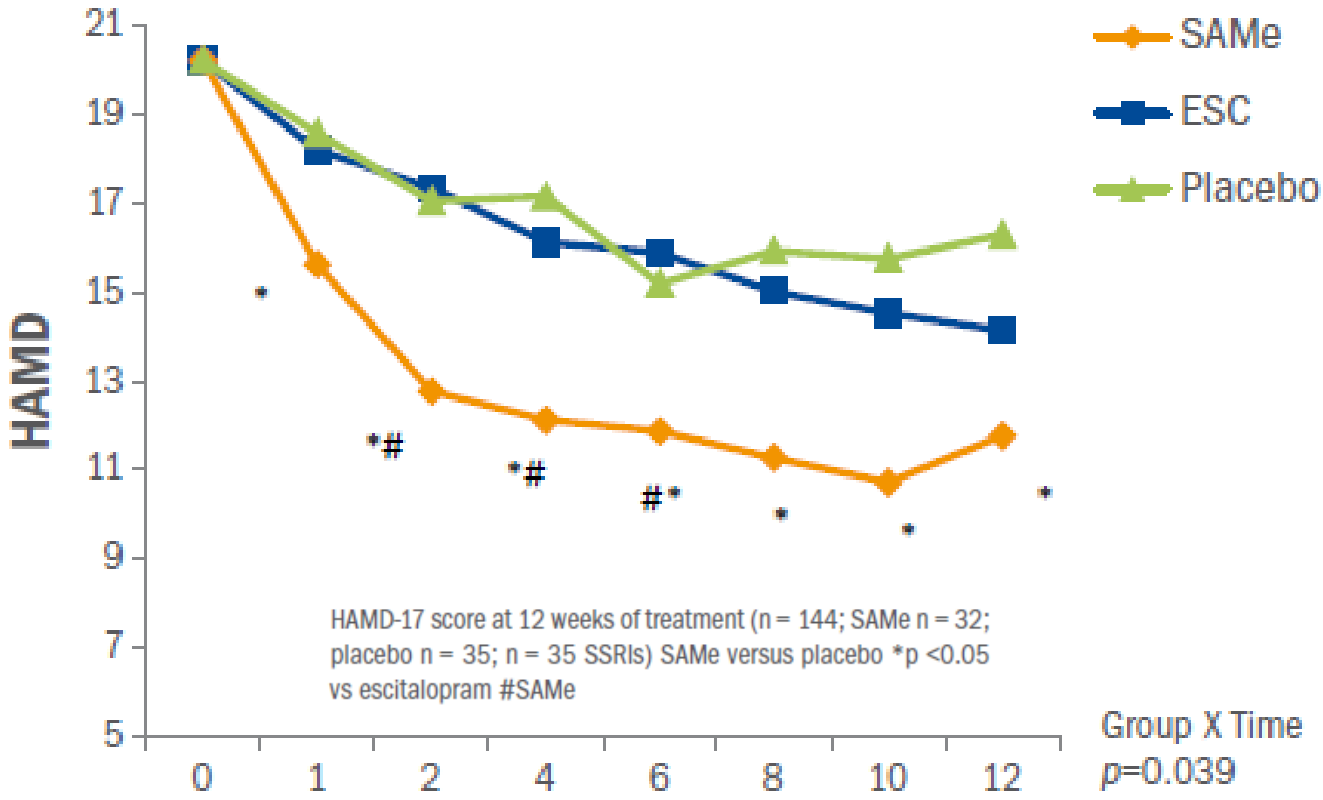
(Mischoulon et al 2014, Sarris et al 2015)

S-αδενόσυλ-L-μεθειονίνη (SAMe)

- Υπερέχει έναντι εικονικού φαρμάκου
- Τουλάχιστον ίδια αποτελεσματικότητα με ιμιπραμίνη, εσιταλοπράμη
- 800-1600mg /ημέρα με γεύμα σε δύο δόσεις
- Α.Ε: αϋπνία, κεφαλαλγία, νευρικότητα

(Mischoulon et al 2014, Sarris et al 2015)

S-αδενόσυλ-L-μεθειονίνη (SAMe)

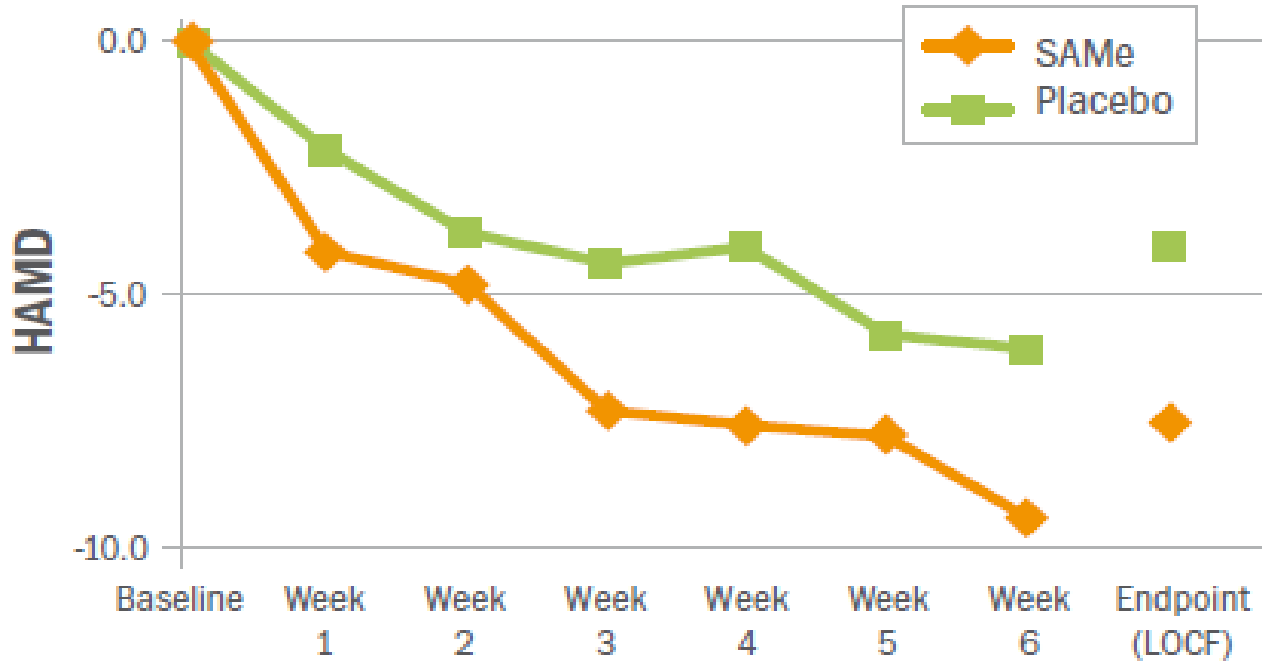


To measure the effectiveness of SAMe as antidepressant, a sample of adults diagnosed with MDD was randomized into treatment groups with SAMe, (800 mg BID) placebo or escitalopram (20 mg).
The effect of SAMe has been statistically significant superior to placebo, according to the primary outcome HAMD-17. Similarly, SAMe was statistically more effective than escitalopram at weeks 2 - 4 - 6.(15, 16)

- Sarris J, I Papakostas G, Vitolo O, Fava M, Mischoulon D. S-adenosyl methionine (SAMe) versus escitalopram and placebo in major depression RCT: Efficacy and effects of histamine and carnitine as moderators of response. J Affect Disord. 2014 Aug;164:76-8.
- Mischoulon D, Price LH, Carpenter LL, Tyrka AR, Papakostas GI, Baer L, Dording CM, Clain AJ, Durham K, Walker R, Ludington E, Fava M. A double-blind, randomized, placebo-controlled clinical trial of S-adenosyl-L-methionine (SAMe) versus escitalopram in major depressive disorder. J Clin Psychiatry. 2014 Apr;75(4):370-6.

S-αδενόσυλ-L-μεθειονίνη (SAMe)

Change in HAM-D Scores During Treatment Among Antidepressant Nonresponders Randomly Assigned to S-Adenosyl Methionine (SAMe) or Placebo



A recent study has evaluated the efficacy of SAMe as adjunctive therapy in patients with MDD. 73 patients not responding to SNRI / SSRIs were included in a randomized, double-blind study lasting 6 weeks. Patients continued during the 6 weeks to be treated with SSRI /SNRI; one of the two groups of randomization was treated with SAMe (400 mg BID), the other with placebo. Both HAMD and the remission rate was higher, with statistically significant power, in patients treated with SAMe.

Papakostas GI, Mischoulon D, Shyu I, Alpert JE, Fava M. S-adenosyl methionine (SAMe) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: a double-blind, randomized clinical trial. Am J Psychiatry. 2010 Aug;167(8):942-8.

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

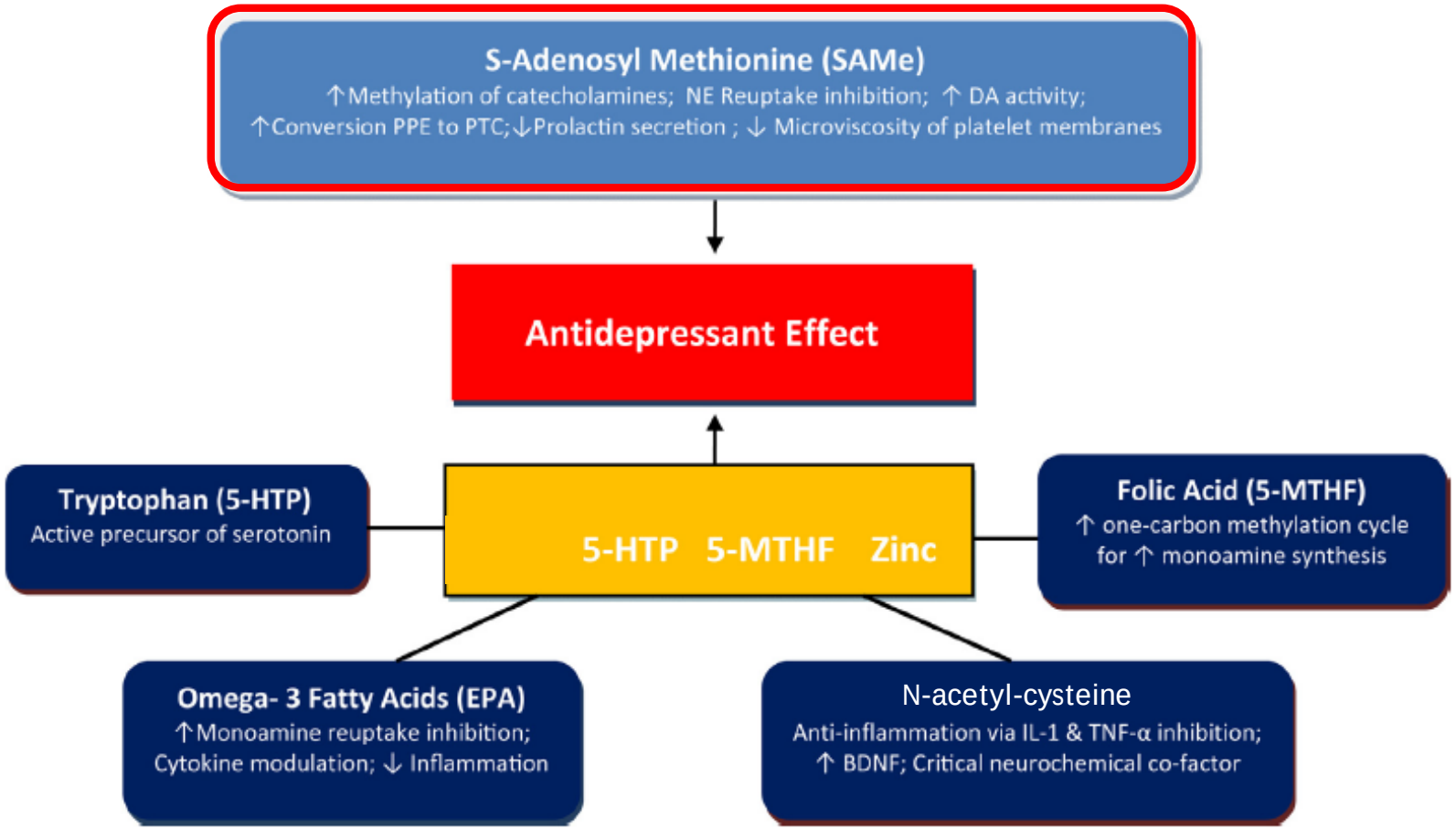
The Canadian Journal of Psychiatry / La Revue Canadienne de Psychiatrie
2016, Vol. 61(9) 576-587

Two systematic reviews found SAM-e effective as a monotherapy versus placebo in mild to severe MDD[61] or versus comparator antidepressants in mild to moderate MDD[81] (Suppl. Table S8). There is also evidence to support adjunctive SAM-e with antidepressants in mild to moderate MDD.[69,81] There are concerns, however, about trial methodologies and paucity of data on SAM-e as maintenance therapy.[61]

Overall, SAM-e is relatively well tolerated, with the most common side effects being gastrointestinal upset, insomnia, sweating, headache, irritability, restlessness, anxiety, tachycardia, and fatigue.[11,81]

In summary, SAM-e is recommended as a second-line adjunctive treatment for use in mild to moderate MDD (Level 1 Evidence) (Table 3).

Αντικαταθλιπτική δράση



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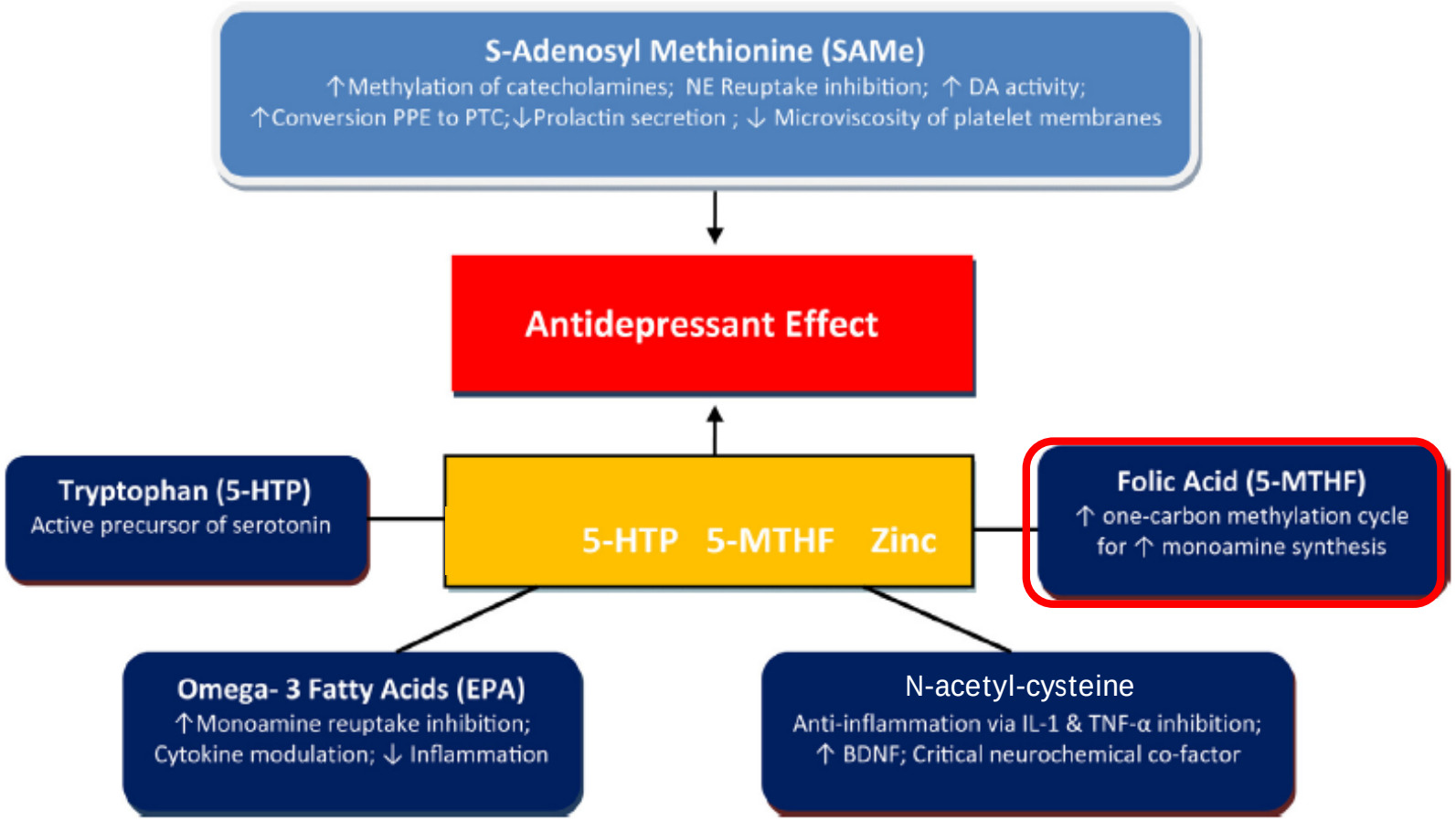

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Φολικό οξύ

BRAINSTORMS
Clinical Neuroscience Update

L-Methylfolate: A Vitamin for Your Monoamines

Stephen M. Stahl, M.D., Ph.D.

Issue: *Synthesis of the monoamine neurotransmitters serotonin, dopamine, and norepinephrine is regulated by L-methylfolate, a derivate of the vitamin folate.*

Folate (vitamin B_9) is well known as one of the 13 essential vitamins, but perhaps what is not as well known is that a derivative of folate—known as L-methylfolate—is actually the active form of the vitamin.[1–3] One of L-methylfolate's critical roles is to regulate the synthesis of the 3 monoamine neurotransmitters serotonin, dopamine, and norepinephrine.[4–6]

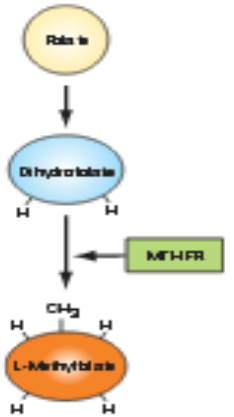
What Is L-Methylfolate?

Folic acid is the synthetic form of the vitamin folate and is present in artificially enriched foods such as bread and in over-the-counter multivitamins as well as in prescription vitamins.[1] Dihydrofolate is the dietary form of folate, derived from green vegetables, yeast, egg yolk, liver, and kidney.[1] A key regulatory enzyme known as methylene tetrahydrofolate reductase or MTHFR (Figure 1)[1–3] converts folic acid or dihydrofolate to a usable form in the body, L-methylfolate, that can then pass through the blood-brain barrier where it modulates the formation of the monoamines serotonin, norepinephrine, and dopamine.[4–6]

How Does L-Methylfolate Regulate the Synthesis of Monoamines?

L-Methylfolate acts to modulate the synthesis of monoamines in a 3-step process (Figure 2). First, L-methylfolate assist in the formation of a critical cofactor, known as tetrahydrobiopterin, or BH4 (Figure 2A) for the synthesis of monoamines.[4–6] Second, BH4 activates the rate-limiting enzymes tyrosine hydroxylase and tryptophan hydroxylase for the synthesis of monoamines.[4–6] Note that when these enzymes lack BH4 (shown as an empty "4" in the blue tyrosine hydroxylase and tryptophan hydroxylase enzymes

Figure 1. Synthesis of L-Methylfolate From Folate



Abbreviations: C = carbon, H = hydrogen, MTHFR = methylene tetrahydrofolate reductase.

Figure 2. Regulation of Monoamine Synthesis by L-Methylfolate

L - μεθυλφολικό

- Φολικό οξύ → L- μεθυλφολικό

↓

παραγωγή σεροτονίνης, νορεπινεφρίνης

- Πολυμορφισμός C677T (ρεντουκτάση του μεθυλφολικού)
- Εμποδίζει μετατροπή φολικού σε μεθυλφολικό

- 70% ασθενών με κατάθλιψη έχουν τον παραπάνω πολυμορφισμό

Φολικό οξύ

Combining Antidepressant Therapies From the Initiation of Treatment: A Paradigm Shift for Major Depression

Stephen M. Stahl, MD, PhD

***Issue:** Combining 2 therapeutic agents from the very initiation of treatment for major depression may lead to enhanced outcomes compared to treatment with a single antidepressant.*

Antidepressants can be life saving, but only about a third of patients attain full remission of their symptoms with their first treatment, and many of these patients relapse despite continuing treatment.[1] Treatment guidelines for major depression generally call for starting a single "first-line" agent and then trying a series of other single agents if the first one is not tolerated or is relatively ineffective.[1] Second and subsequent treatments are progressively less likely to lead to full remission of symptoms, and for those treatments that do lead to remission, they are progressively less likely to sustain that remission for more than a few months.[1] In order to target greater sustained remission rates from a major depressive episode, a paradigm shift is afoot in which the chances of a first treatment working are maximized by giving combinations of treatments from the time the first antidepressant therapy is initiated (eTable 1).[2]

Are 2 or More Therapeutic Mechanisms Better Than 1?

Some antidepressants have a single major mechanism of therapeutic action, and others have 2 or more.[1–6] These latter drugs are sometimes called multifunctional, with recent theories suggesting that multiple mechanisms of antidepressant action in a single drug are better than a single mechanism.[3–7] Multifunctional actions can also be created by combining 2 drugs with clearly different mechanisms. Numerous investigations are now ongoing to determine whether, from the initiation of antidepressant therapy, the combination of drugs works better than either agent alone.[2,8,10]

Antidepressants Plus Antidepressants

The landmark study by Nelson et al[8] showed that the combination of the SSRI (selective serotonin reuptake inhibitor) fluoxetine with the norepi nephrine reuptake inhibitor desipra mine in non–treatment-resistant inpa tients with a major depressive episod was significantly more likely to result i remission than was fluoxetine alone o desipramine alone.[8] Blier et al[9,10] are als conducting a series of very novel studie of antidepressant combinations, show ing in 1 study that remission rates of pa tients taking the SSRI paroxetine + mir tazapine were double the rates of thos taking the single drugs.[9] Further stud ies by this group suggest that remissio rates with several combinations of an tidepressants also roughly doubled th remission rates with a single agent (spe cifically, mirtazapine + either fluoxetine, venlafaxine, or bupropion vs fluoxetine alone).[10] These very promising findings are now being followed up by a major study funded by the NIMH Combining Oral Medications to End Depression (COMED) on the Depression Trials Network comparing the potential benefits of combining any 2 of the agents at initiation of treatment: bupropion, escitalopram, mirtazapine, or venlafaxine. If these results replicate the doubling of remission rates, there will most likely be a rapid shift to using 2 agents from initiation of treatment for a major depressive episode.

Antidepressants Plus Methylfolate/Folate

One of the first agents conceptualized to be a combination therapy from the initiation of treatment of major depression was the natural product folic acid and its centrally active natural derivate methylfolate. Three randomized controlled trials[11,12,14] have shown superior efficacy of antidepressant and folate/methylfolate combinations from initiation of therapy compared to antidepressants alone.

In the first such study,[11] depressed patients specifically with low red blood cell (RBC) folate levels were given treatment as usual in the pre-SSRI era and randomized to either 15 mg/d of racemic methylfolate or placebo from the initiation of therapy. Serum and RBC folate levels increased, and clinical measures of mood improved significantly more in the antidepressant + methylfolate group

Brainstorms is a section of The Journal of Clinical Psychiatry aimed at providing updates of novel concepts emerging from the neurosciences that have relevance to the practicing psychiatrist.

From the Neuroscience Education Institute in Carlsbad, California, and the Department of Psychiatry at the University of California San Diego.

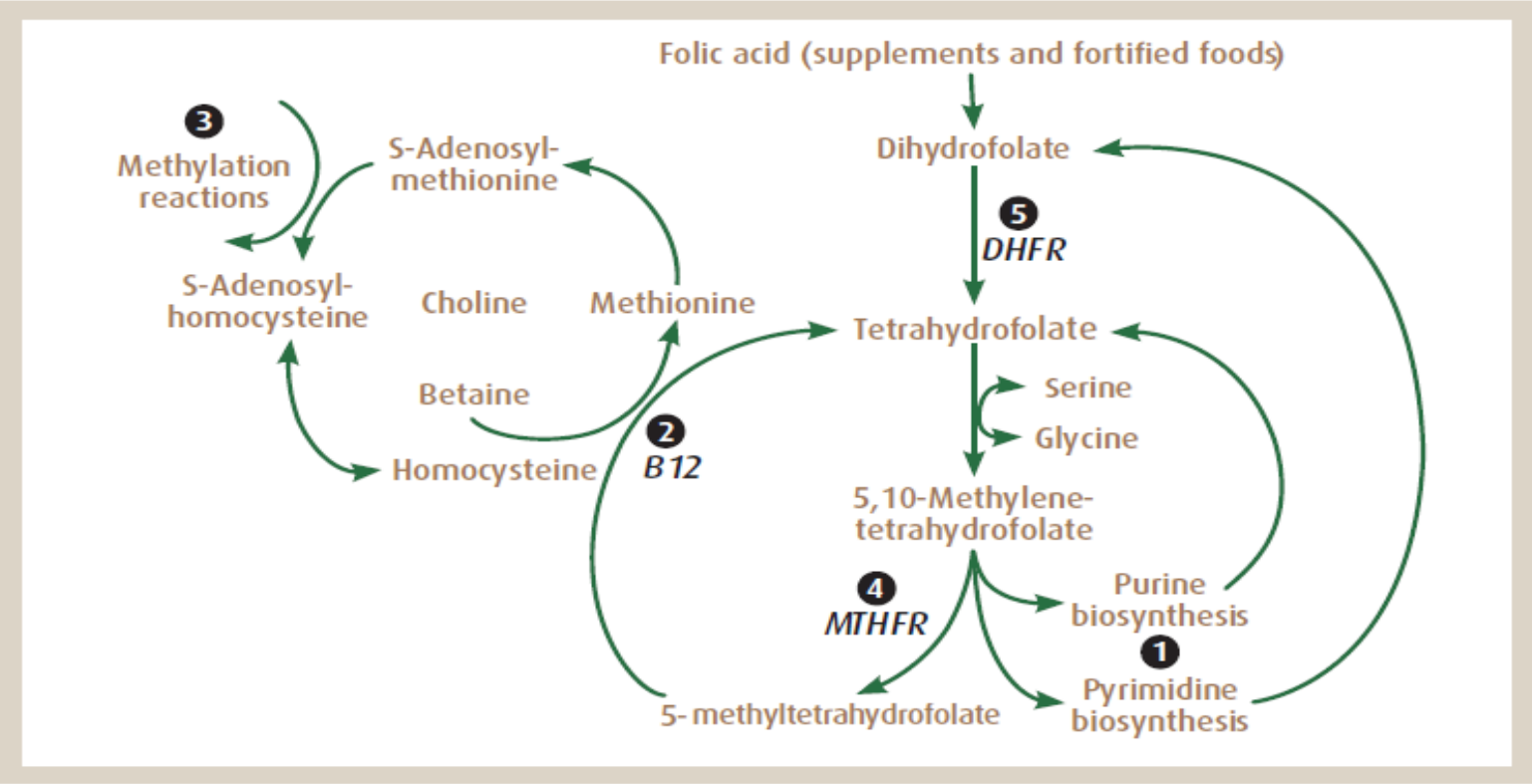
For reprint and financial disclosure information, go to www.psychiatrist.com/brainstorms.

doi:10.4088/JCP.09bs05697blu

Supplementary material: eTable 1 is available at www.psychiatrist.com.

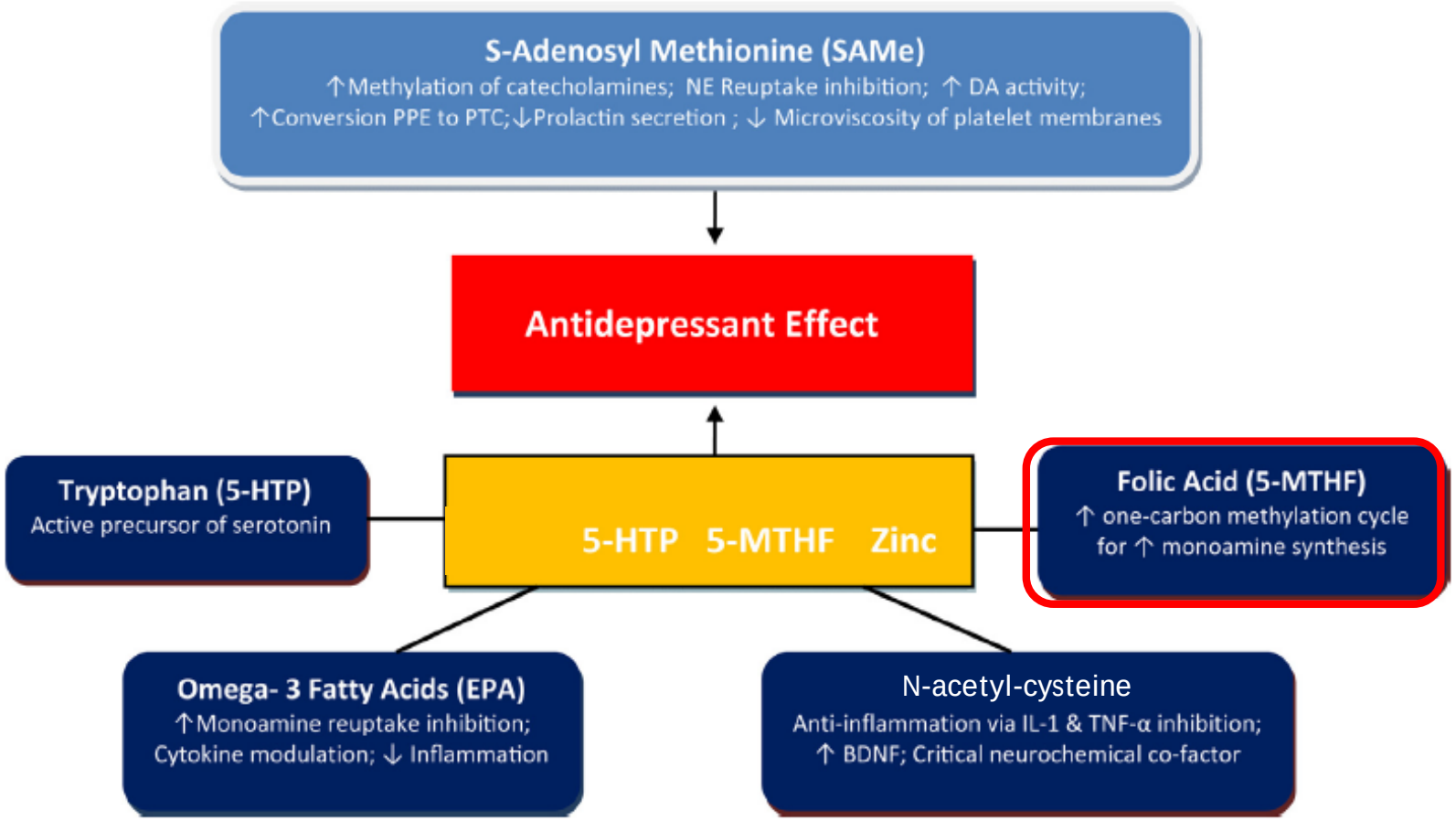
L - μεθυλφολικό

Principal Components of the Folate Biochemical Cycle.



Principal Components of the Folate Biochemical Cycle. Abbreviations: DHFR = dihydrofolate reductase; MTHFR = methylenetetrahydrofolate reductase. Reactions: 1 - Biosynthesis of nucleotides for incorporation into DNA and RNA; 2 - Remethylation of homocysteine to form methionine (vitamin B12 serves as a coenzyme in this reaction); 3 - Methylation of substrates, including DNA, RNA, phospholipids, and proteins; 4 - MTHFR, which catalyzes the formation of 5-methyltetrahydrofolate needed for methylation reactions; 5 - Dihydrofolate reductase enzyme.

Αντικαταθλιπτική δράση



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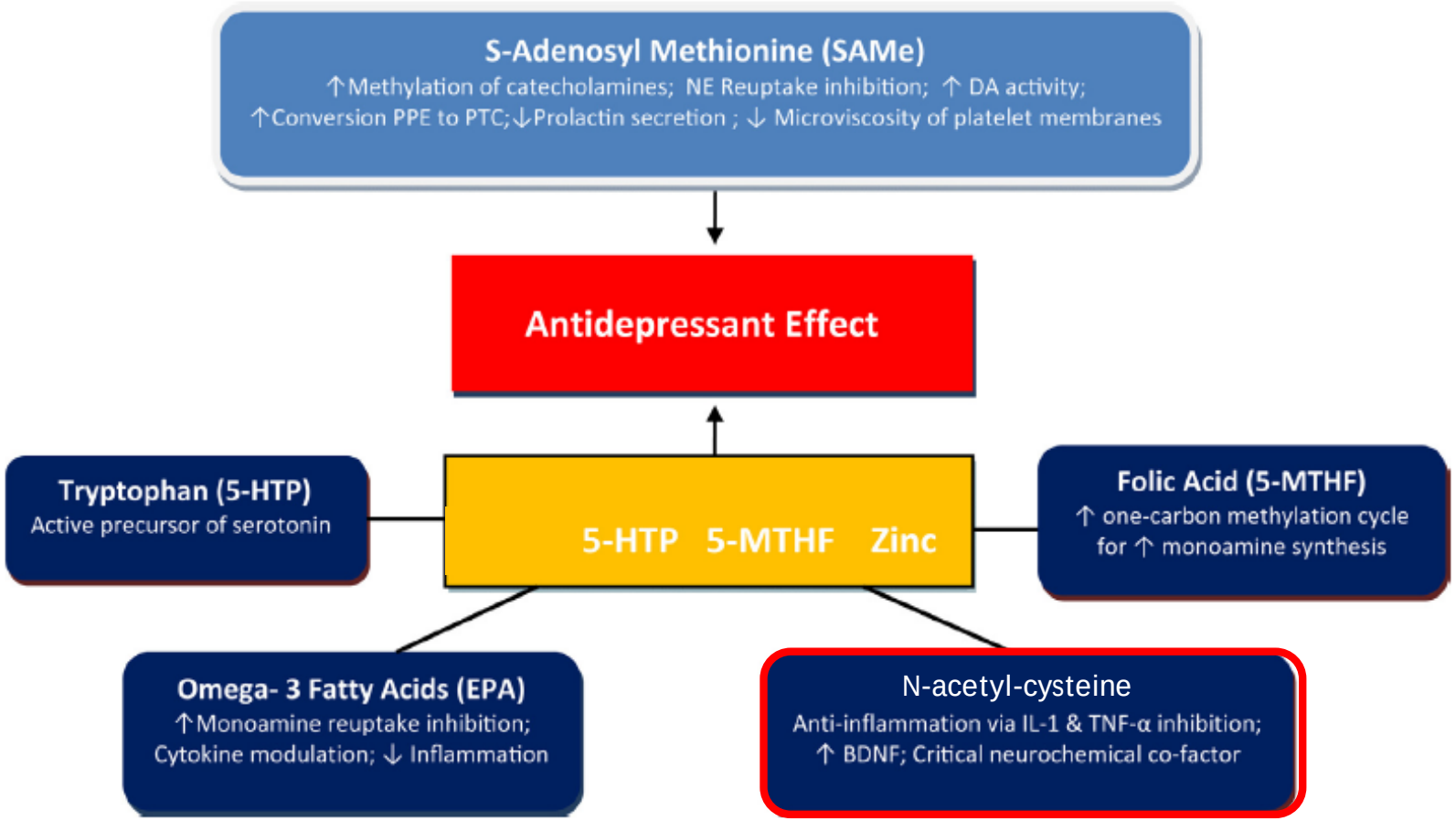

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N - ακετυλοκυστεΐνη

- Παράγωγο του αμινοξέως κυστεΐνης
- Ρυθμιστής γλουταμικού στη σύναψη, αυξάνει γλουταθειόνη
- Οξειδωτικό stress, νευρογένεση, κυτταρική απόπτωση, μιτοχονδριακή δυσλειτουργία, νευροανασολογία, δυσρύθμιση γλουταμινεργικής και ντοπαμινεργικής λειτουργίας

(Samuni et al 2013, Deepmala et al 2015)

N-ακετυλοκυστεΐνη

Neuroscience and Biobehavioral Reviews 55 (2015) 294–321

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

Clinical trials of N-acetylcysteine in psychiatry and neurology: A systematic review

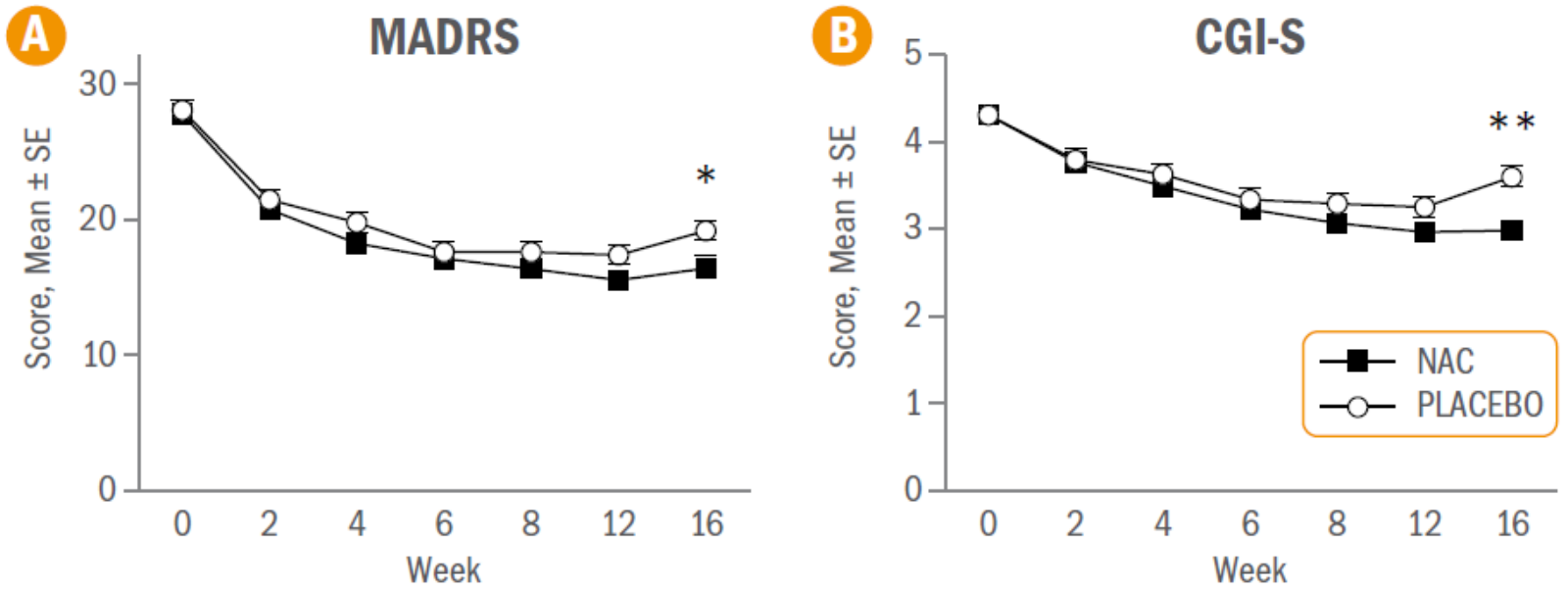
Deepmala[a,b,*], John Slattery[a,c], Nihit Kumar[a,b], Leanna Delhey[a,c], Michael Berk[d,e], Olivia Dean[d,e], Charles Spielholz[f], Richard Frye[a,c]

Overall ratings of NAC based on clinical studies presented by condition.

Psychiatric and neurological condition	Uncontrolled studies Positive% (positive/total)	Controlled studies Positive% (positive/total)	Grade of recommendation	Recommendation for treatment
Addiction – cannabis	50%(0.5/1)	50%(0.5/1)	B	Mixed
Addiction – cocaine	100%(1/1)	50%(1.5/3)	B	Mixed
Addiction – methamphetamine		25%(0.5/2)	B	No
Addiction – nicotine		33%(2/6)	B	No
Addiction – pathological gambling	100%(1/1)	25%(0.5/2)	B	No
Alzheimer's disease	100%(2/2)	50%(0.5/1)	C	Mixed
Amyotrophic lateral sclerosis	50%(1/2)	0%(0/2)	B	No
Anxiety	100%(1/1)		D – SC	None
Attention-deficit hyperactivity disorder		100%(1/1)	C	None
Autism	100%(2/2)	50%(1.5/3)	B	Mixed
Bipolar disorder	100%(1/1)	50%(1/2)	A	Mixed
Depressive disorder	100%(1/1)	50%(0.5/1)	B	Mixed
Epilepsy	75%(3/4)		C	Mixed
Impulse control-nail biting	100%(2/2)	50%(0.5/1)	C	Mixed
Impulse control-skin picking	100%(4/4)		C	Mixed
Impulse control-trichotillomania	100%(4/4)	50%(1/2)	B	Mixed
Neuropathy	100%(1/1)	100%(1/1)	C	Mixed
Obsessive compulsive disorder	100%(1/1)	50%(0.5/1)	C	Mixed
Schizophrenia	100%(1/1)	75%(1.5/2)	B	Mixed
Traumatic brain injury		100%(1/1)	B	None

SC, Single Case Report.

N-ακετυλοκυστεΐνη



252 patients with an episode of moderate to severe MDD, diagnosed according to DSM-IV were treated with NAC (500 mg BID) or placebo in addition to standard treatment and followed for 16 weeks. The study is a double-blind, randomized, placebo-controlled trial. The primary outcome measure, the Montgomery Asberg Depression Rating Scale (MADRS), was significant at 16th week for the complete pool (Fig. A). However for participants with a MADRS> 25 at baseline, the significance stretched at weeks 6, 8, 12, 16 ($p < 0.05$). Also for the CGI scale (Fig. B) the results are statistically significant at week 16.

Berk M, Dean OM, Cotton SM, Jeavons S, Tanious M, Kohlmann K, Hewitt K, Moss K, Allwang C, Schapkaitz I, Robbins J, Cobb H, Ng F, Dodd S, Bush AI, Malhi GS. The efficacy of adjunctive N-acetylcysteine in major depressive disorder: a double-blind, randomized, placebo-controlled trial. J Clin Psychiatry. 2014 Jun;75(6):628-36.

N-ακετυλοκυστεΐνη

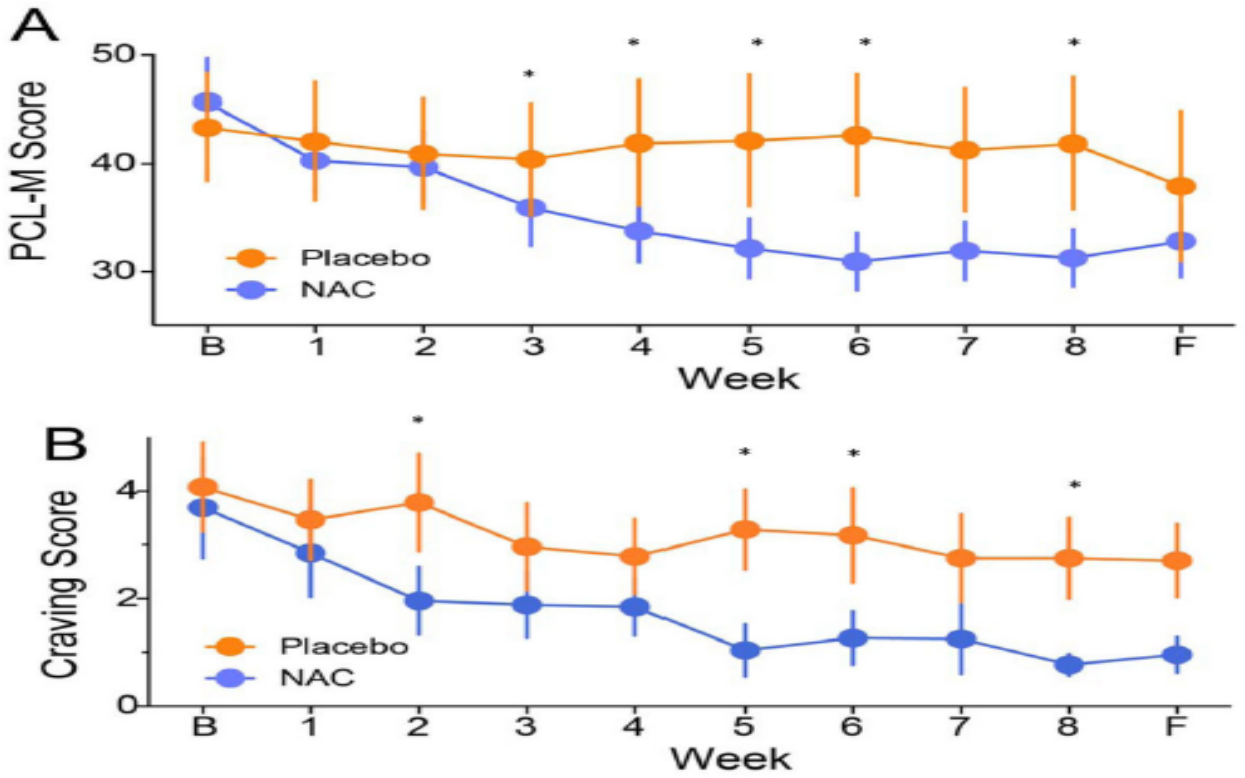


Figure 2. Change in PTSD Symptoms and Drug Craving Over Time by Treatment Condition
A) Weekly total score on the PTSD Military Checklist (PCL-M). NAC (N-acetylcysteine) showed a significant treatment effect to reduce PTSD symptoms over the 8-week treatment period. Follow-up measure was obtained 4 weeks after discontinuing NAC or placebo (i.e., week 12 of the study) **B)** Weekly subjective craving score measured using a Visual Analog Scale (VAS). NAC showed a significant treatment effect to reduce drug craving over the 8-week treatment period. *$p<.05$. B = Baseline, F = Follow-Up.

Back et al. *J Clin Psychiatry*. 2016 November ; 77(11): e1439–e1446. doi:10.4088/JCP.15m10239.

N-acetylcysteine in depressive symptoms and functionality: a systematic review and meta-analysis

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Aims: To assess the utility of n-acetylcysteine (NAC) for depressive symptoms in psychiatric conditions.

Methods: A computerized literature search was conducted in Medline, Embase, the Cochrane Library, Scielo, PsycINFO, Scopus, and Web of Knowledge. No year or country restrictions were used. The Boolean terms used for the electronic database search were: (NAC OR n-acetylcysteine OR acetylcysteine) AND (depression OR depressive OR depressed) AND (trial). The last search was performed in November of 2014. Double-blind, randomized, placebo-controlled trials using NAC for depressive symptoms regardless the main psychiatric condition. Using keywords and cross-referenced bibliographies, 38 studies were identified and examined in depth. Of those, 33 articles were rejected because inclusion criteria were not met. Finally, 5 studies were included. Data were extracted independently by 2 investigators. The primary outcome measure was change in depressive symptoms. Functionality, quality of life, manic and anxiety symptoms were also examined. A full review and meta-analysis were performed. Standardized mean differences (SMDs) and Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

Results: Five studies fulfilled our inclusion criteria for the meta-analysis, providing data on 574 participants, of whom 291 were randomised to receive NAC, and 283 to placebo. The follow-up varied from 12 to 24 weeks. Two studies included subjects with BD and current depressive symptoms, one subjects with MDD in a current depressive episode, and two subjects with depressive symptoms in the context of other psychiatric condition (one trichotillomania and one heavy smoking). Treatment with NAC improved depressive symptoms as assessed by MADRS and HDRS when compared to placebo (SMD = 0.37, 95% CI 0.19 to 0.55, $p < 0.001$). Subjects receiving NAC presented better scores regarding the CGI-S of depressive symptoms at the follow-up than subjects on placebo (SMD = 0.22, 95% CI 0.03 to 0.41, $p < 0.001$). In addition, global functionality was better in NAC than in placebo. There were no changes in quality of life. With regard to side effects, only minor side effects were associated with NAC (OR 1.61, 95% IC 1.01 to 2.59, p = 0.049).

Conclusions: NAC ameliorates depressive symptoms and improves functionality, with a relatively moderate impact and good tolerability.

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BMC Medicine

OPINION Open Access

Cognitive remission: a novel objective for the treatment of major depression?

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Table 1 Potential therapeutic targets for the treatment of cognitive dysfunction in major depressive disorder (MDD)

Agent	Putative mechanisms of action	Clinical evidence [Ref. No.]
Vortioxetine	5-HT_3/$5HT_7$ receptor antagonist; partial agonist at the 5-HT_{1B} receptor; agonist at 5-HT1A receptor; inhibitor of the 5-HT transporter	Two multicenter RCTs having cognitive performance as the primary outcome measure were conducted in participants with MDD [91, 92]. Overall, vortioxetine displayed a significant procognitive effect over several domains, which was largely independent of the amelioration of affective symptoms. However, a recent meta-analysis found that the overall effect size was small (0.34) [20].
Lisdexamfetamine dimesylate	D-amphetamine prodrug; enhances the efflux of dopamine and norepinephrine in the CNS	A RCT found LDX augmentation to be efficacious in reducing self-reported executive dysfunction among participants with MDD (N = 143) with residual depressive symptoms [94].
Erythropoietin	Readily crosses the BBB and increases the production of BDNF	EPO improved verbal learning and memory in a preliminary RCT involving participants with treatment-resistant MDD (N = 40) [97]. This effect was largely mood-independent. However, cognitive performance was not the primary outcome measure in this trial.
Minocycline	Promotes hippocampal neurogenesis; Anti-apoptotic effects; Anti-inflammatory activity; Antioxidant; Modulates glutamatergic transmission; Stabilizes the microglia	No clinical trial has investigated the potential procognitive effects of minocycline in samples with MDD.
Thiazolidinediones	Antagonist of PPAR-gamma; increased the production of BDNF; has anti-inflammatory and antioxidant activities	No published clinical trial has investigated the effects of thiazolidinediones upon cognition in samples with MDD.
S-adenosyl methionine	Major methyl-donor; essential for the synthesis of several neurotransmitters; involved in the synthesis of glutathione	A post-hoc analysis of a preliminary RCT involving 40 SSRI-resistant participants with MDD found SAMe to improve in self-rated recall and word-finding difficulties compared to
Omega-3 PUFAs	Anti-inflammatory and antioxidant activities; Increases the production of BDNF; diminishes microglia-related neuro-inflammation	No published clinical trials to date have investigated the effects of omega-3 PUFAs on cognitive performance in samples with MDD.
Modafinil	Pleotropic agent that targets several neurotransmitter systems (e.g., 5-HT, GABA, glutamate, orexin, and histamine).	A small open-label trial has found that modafinil augmentation improved executive function in a sample with MDD [147].
Galantamine	Rapidly reversible acetylcholinesterase inhibitor and a potent modulator of the nicotinic receptor; affects monoamines, GABA and glutamate neurotransmitter systems.	Two preliminary RCTs have found no evidence for a procognitive effect of galantamine augmentation in participants with MDD [150, 151].
Scopolamine	Potent muscarinic antagonist; modulates 5-HT, neuropeptide Y, dopaminergic, and glutamatergic systems	A proof-of-concept RCT did not observe significant effects of scopolamine in a task measuring sustained attention in a sample with MDD [154]
N-acetylcysteine	Pleotropic agent that modulates glutamate transmission; antioxidant; anti-inflammatory effect; anti-apoptotic activity; increases glutathione.	No published trial has investigated the effects of NAC on cognitive function in samples with MDD.
Statins	Increases BDNF; antioxidant; anti-inflammatory; inhibits the enzyme IDO; modulates the microglia.	No published trial has investigated potential procognitive effects of statins in samples with MDD.

Κατευθυντήριες οδηγίες και nutraceuticals…

Table 3. Summary of Recommendations for Natural Health Products.

Intervention	Indication	Recommendation	Evidence	Monotherapy or Adjunctive Therapy
St. John's wort	Mild to moderate MDD	First line	Level 1	Monotherapy
	Moderate to severe MDD	Second line	Level 2	Adjunctive
Omega-3	Mild to moderate MDD	Second line	Level 1	Monotherapy or adjunctive
	Moderate to severe MDD	Second line	Level 2	Adjunctive
SAM-e	Mild to moderate MDD	Second line	Level 1	Adjunctive
	Moderate to severe MDD	Second line	Level 2	Adjunctive
Acetyl-L-carnitine	Mild to moderate MDD	Third line	Level 2	Monotherapy
Crocus sativus (saffron)	Mild to moderate MDD	Third line	Level 2	Monotherapy or adjunctive
DHEA	Mild to moderate MDD	Third line	Level 2	Monotherapy
Folate	Mild to moderate MDD	Third line	Level 2	Adjunctive
Lavandula (lavender)	Mild to moderate MDD	Third line	Level 3	Adjunctive
Inositol	Mild to moderate MDD	Not recommended	Level 2	
Tryptophan	Mild to moderate MDD	Not recommended	Level 2	
Rhodiola rosea (roseroot)	Mild to moderate MDD	Not recommended	Insufficient evidence	

DHEA, dehydroepiandrosterone; MDD, major depressive disorder; SAM-e, S-adenosyl-L-methionine.

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

The Canadian Journal of Psychiatry / La Revue Canadienne de Psychiatrie 2016, Vol. 61(9) 576-587

Παθοφυσιολογία της κατάθλιψης

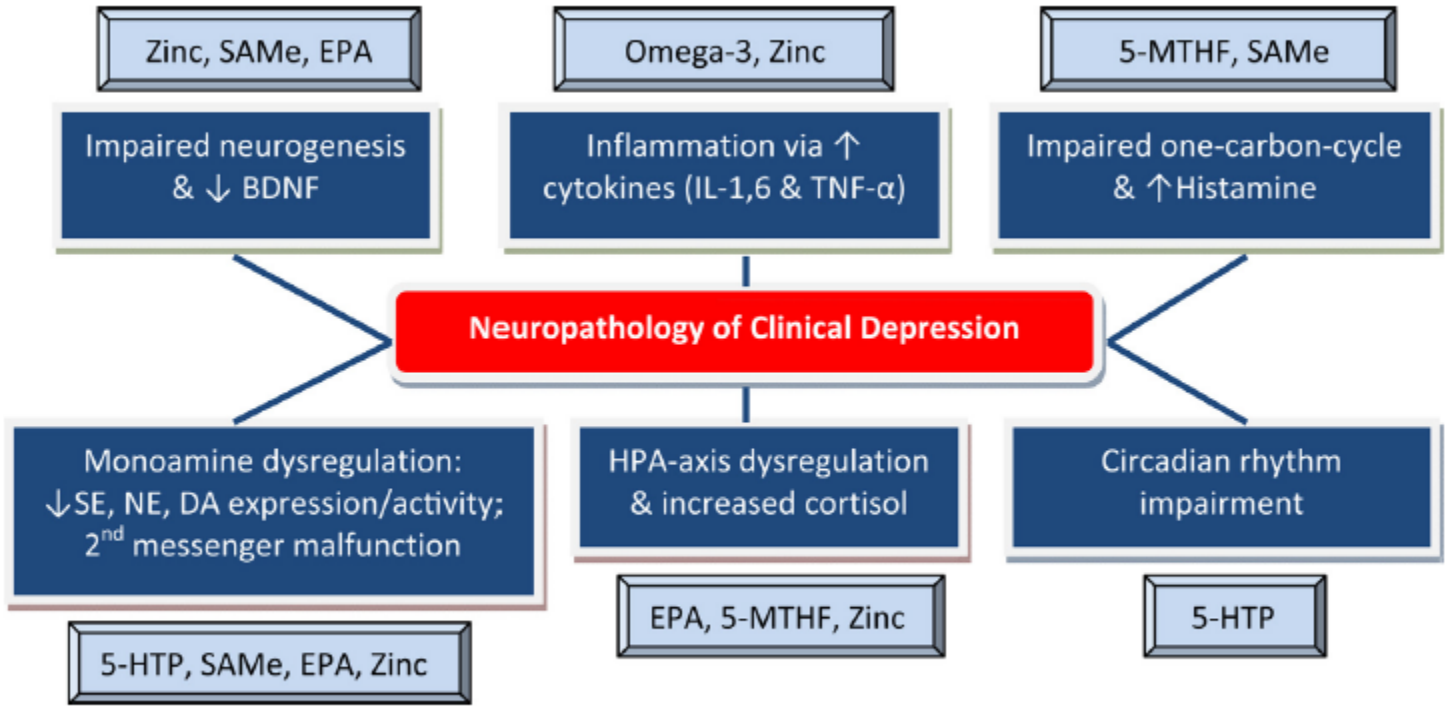

Fig. 1. Pathophysiology of depression and the nutraceuticals modulating these neurochemical pathways.

Sarris et all, An adjunctive antidepressant nutraceutical combination in treating major depression: Study protocol, and clinical considerations - Advances in Integrative Medicine 2 (2015) 49–55

Σας ευχαριστώ πολύ!