Physical activity as antidepressant

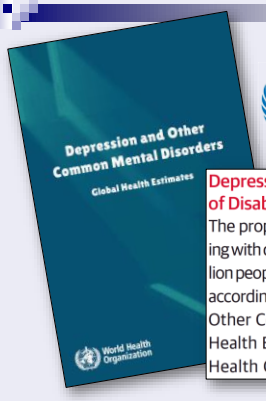
How good is it and why hasn't my doctor told me about it?

Panteleimon Ekkekakis, Ph.D., FACSM, FNAK

MICHIGAN STATE UNIVERSITY

1

JAMA April 18, 2017 Volume 317, Number 15 1517



World Health Organization

Depression Is the Leading Cause of Disability Around the World

The proportion of the global population living with depression is estimated to be 322 million people—4.4% of the world's population—according to a new report, "Depression and Other Common Mental Disorders: Global Health Estimates," released by the World Health Organization. The report also in-

2

Journal of Affective Disorders 193 (2016) 203–207

Mortality and life expectancy in persons with severe unipolar depression

Thomas Munk Laursen [a,*], Katherine L. Musliner [a,b], Michael E Benros [c], Mogens Vestergaard [d], Trine Munk-Olsen [a]

Mortality Rate Ratio: **2.07**

Methods: We followed a Danish population-based cohort from 1995–2013 ($N = 5{,}103{,}699$). The cohort included all residents in Denmark during the study period. Mortality rate ratios (MRRs) and life expectancy in persons with unipolar depression were calculated using survival analysis techniques.
Results: The overall MRR was 2.07 (95% Confidence Interval (CI): 2.05–2.09) in people with a previous unipolar depression diagnosis compared to the general Danish population. This excess mortality translated into a reduced life expectancy of 14.0 years in men and 10.1 years in women (assuming onset at age 15). The MRR was highest for death due to suicide and accidents (MRR: 4.66; 95% CI: 4.53–4.79), but the absolute number of deaths was highest for natural cau

Life Expectancy Difference:
14 years in men
10 years in women

4

British Journal of Psychiatry (2013) 203, 90–102

Adjusted prognostic association of depression following myocardial infarction with mortality and cardiovascular events: individual patient data meta-analysis

A. Meijer, H. J. Conradi, E. H. Bos, M. Anselmino, R. M. Carney, J. Denollet, F. Doyle, K. E. Freedland, S. L. Grace, S. H. Hosseini, D. A. Lane, L. Pilote, K. Parakh, C. Rafanelli, H. Sato, R. P. Steeds, C. Welin and P. de Jonge

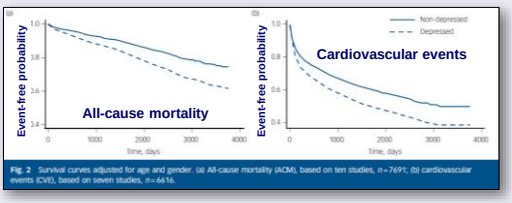


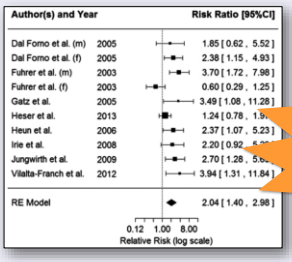
Fig. 2 Survival curves adjusted for age and gender. (a) All-cause mortality (ACM), based on ten studies, $n = 7691$; (b) cardiovascular events (CVE), based on seven studies, $n = 6616$.

5

BMJ Open 2015;**5**:e008853

Dementia risk estimates associated with measures of depression: a systematic review and meta-analysis

Nicolas Cherbuin, Sarang Kim, Kaarin J Anstey



RR for risk of Alzheimer's: 2.04

6

So, what's the cause of depression?

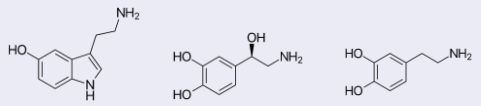
7

Brit. J. Psychiat. (1967), 113, 1237–1264

The Biochemistry of Affective Disorders

By ALEC COPPEN

There is growing evidence of a causal association between brain monoamines and affective disturbances; if brain monoamines are depleted by



Serotonin Norepinephrine Dopamine

8

N Engl J Med 2008;358:55-68

Major Depressive Disorder

R.H. Belmaker, M.D., and Galila Agam, Ph.D.

THE MONOAMINE-DEFICIENCY HYPOTHESIS

increase the availability of neurotransmitters. These discoveries led to a major theory of depression known as the monoamine-deficiency hypothesis. Numerous studies of norepinephrine and serotonin metabolites in plasma, urine, and cerebrospinal fluid, as well as postmortem studies of the brains of patients with depression, have yet to identify the purported deficiency reliably. However, a newly dis-

9

Neuroscience and Biobehavioral Reviews 51 (2015) 164–188

Is serotonin an upper or a downer? The evolution of the serotonergic system and its role in depression and the antidepressant response

Paul W. Andrews [a,*], Aadil Bharwani [a], Kyuwon R. Lee [a], Molly Fox [b], J. Anderson Thomson Jr. [c,d]

6. Conclusion and future directions

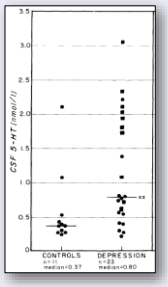
The reigning paradigm conceptualizes depression as a state of reduced serotonin transmission. In this paper we have reviewed a large body of evidence indicating that the opposite appears to be true. For the depressive phenotypes we have considered—sickness behavior, starvation depression, and melancholia—serotonin transmission to multiple brain regions appears to be elevated. Others have suggested serotonin transmission is elevated in depression (Andrews and Thomson, 2009; Petty et al., 1994; Zangen et al., 1997), but this is the first in-depth review of the high serotonin hypothesis.

10

Journal of Affective Disorders, 12 (1987) 13–22

5-HT and 5-HIAA in cerebrospinal fluid in depression

Annette Gjerris [1], Anne Stub Sørensen [1], Ole J. Rafaelsen [1], Lene Werdelin [2], Christer Alling [3] and Markku Linnoila [4]



11

Molecular Psychiatry

The serotonin theory of depression: a systematic umbrella review of the evidence

Joanna Moncrieff[1,2][*], Ruth E. Cooper[1], Tom Stockmann[4], Simone Amendola[5], Michael P. Hengartner[6] and Mark A. Horowitz[1,2]

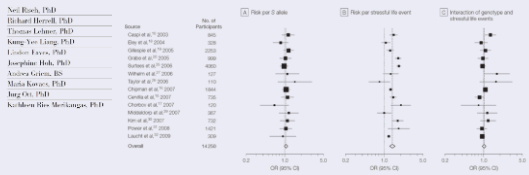
Our comprehensive review of the major strands of research on serotonin shows there is no convincing evidence that depression is associated with, or caused by, lower serotonin concentrations or activity. Most studies found no evidence of reduced serotonin activity in people with depression compared to people without, and methods to reduce serotonin availability using tryptophan depletion do not consistently lower mood in volunteers. High quality, well-powered genetic studies effectively exclude an association between genotypes related to the serotonin system and depression, including a proposed interaction with stress.

12

JAMA. 2009;301(23):2462-2471

Interaction Between the Serotonin Transporter Gene (*5-HTTLPR*), Stressful Life Events, and Risk of Depression

A Meta-analysis



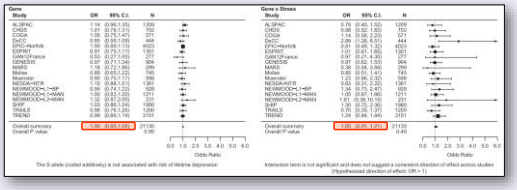
Conclusion This meta-analysis yielded no evidence that the serotonin transporter genotype alone or in interaction with stressful life events is associated with an elevated risk of depression in men alone, women alone, or in both sexes combined.

13

Molecular Psychiatry (2018) 23, 133–142

Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression

RC Culverhouse[1], NL Saccone[2], AC Horton[3], Y Ma[3], KJ Anstey[4], T Banaschewski[5], M Burmeister[6,7], S Cohen-Woods[8], B Etain[9,10,11], HL Fisher[12], N Goldman[13], S Guillaume[14,15,16], J Horwood[17], G Juhasz[18,19,20,21], KJ Lester[22], L Mandelli[23], CM Middeldorp[24,25], E Ollié[14,15,16], S Villafuerte[6], TM Air[26], R Araya[27], L Bowes[28], R Burns[4], EM Byrne[29], C Coffey[30], WL Coventry[31], KAB Gawronski[32], D Glei[33], A Hatzimanolis[34,35], J-J Hottenga[24,36], I Jaussent[14], C Jawahar[26], C Jennen-Steinmetz[37], JR Kramer[38], M Lajnef[39], K Little[40,41], HM zu Schwabedissen[42], M Nauck[43], E Nederhof[44], P Petschner[19,21,45], WJ Peyrot[46], C Schwahn[47], G Sinnamon[26], D Stacey[26], Y Tian[48], C Toben[49], S Van der Auwera[50], N Wainwright[30], J-C Wang[51], G Willemsen[24,36], IM Anderson[20,52], V Arolt[53], C Åslund[54,55], G Bagdy[19,21,45], BT Baune[26], F Bellivier[9,10,11], DI Boomsma[24,25,36], P Courtet[14,15,16], U Dannlowski[53], EJC de Geus[24,36], JFW Deakin[20,52], S Eastwood[56], T Eley[57], DM Ferguson[17], AM Goate[51], X Gonda[19,21,45,58], HJ Grabe[49], C Holzman[59], EO Johnson[60], M Kennedy[61], M Lauchs[62], NG Martin[63], MR Munafò[62,64], KW Nilsson[54,55], AJ Oldehinkel[44], CA Olsson[65,66,67], J Ormel[44], C Otte[47], GC Patton[68], BWJH Penninx[46], K Ritchie[12], M Sarchiapone[69], JM Scheid[70], A Serretti[23], JH Smit[46], NC Stefanis[34,35], PG Surtees[30], H Wölzke[71], M Weinstein[33], M Whooley[72], JI Nurnberger Jr[73], N Breslau[48] and LJ Bierut[1]

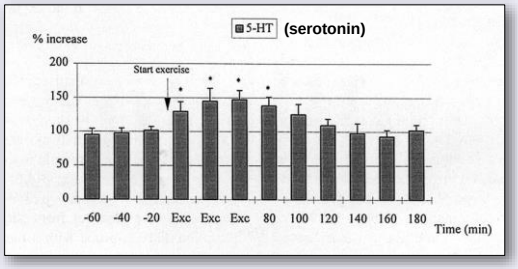


14

Brain Research 740 (1996) 245–252

Effects of tryptophan and/or acute running on extracellular 5-HT and 5-HIAA levels in the hippocampus of food-deprived rats

Romain Meeusen [a,*], Katrien Thorré [b], Francis Chaouloff [d], Sophie Sarre [b], Kenny De Meirleir [a], Guy Ebinger [c], Yvette Michotte [b]



17

So, how do we measure depression?

18

Journal of Affective Disorders 233 (2018) 3–14

Peripheral biomarkers of major depression and antidepressant treatment response: Current knowledge and future outlooks

Bharathi S. Gadad, Manish K. Jha, Andrew Czysz, Jennifer L. Furman, Taryn L. Mayes, Michael P. Emslie, Madhukar H. Trivedi*

results have been validated in additional patient cohorts, however. As a result, no individual or collection of biomarkers have translated into clinical practice for either diagnosis of depression or guidance of treatment selection. The heterogeneous pathology driving depression makes biomarker discovery particularly challenging, though provides

19

20

Hamilton Rating Scale for Depression

1 **DEPRESSED MOOD** *(sadness, hopeless, helpless, worthless)*
- 0 |__| Absent.
- 1 |__| These feeling states indicated only on questioning.
- 2 |__| These feeling states spontaneously reported verbally.
- 3 |__| Communicates feeling states non-verbally, i.e. through facial expression, posture, voice and tendency to weep.
- 4 |__| Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.

2 **FEELINGS OF GUILT**
- 0 |__| Absent.
- 1 |__| Self reproach, feels he/she has let people down.
- 2 |__| Ideas of guilt or rumination over past errors or sinful deeds.
- 3 |__| Present illness is a punishment. Delusions of guilt.
- 4 |__| Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

HRSD
Range: 0-52

21

Beck Depression Inventory

0. I do not feel sad.
1. I feel sad.
2. I am sad all the time and can't snap out of it.
3. I am so sad or unhappy that I can't stand it.

0. I am not particularly discouraged about the future.
1. I feel discouraged about the future.
2. I feel I have nothing to look forward to.
3. I feel that the future is hopeless and that things cannot improve.

22

So, how do we treat depression?

23

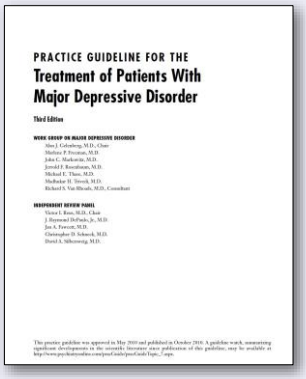
DEPRESSION

Psychotherapy | **Pharmacotherapy**

(Plus magnetic neurostimulation, electroconvulsive therapy)

24

2010



PRACTICE GUIDELINE FOR THE
Treatment of Patients With Major Depressive Disorder
Third Edition

AMERICAN PSYCHIATRIC ASSOCIATION

25

2010

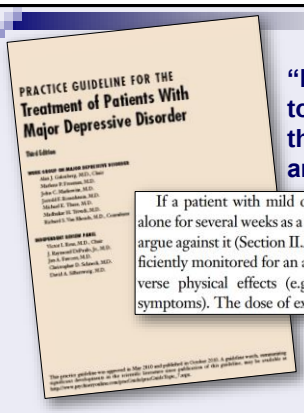
Modality

Severity of Illness	Pharmacotherapy	Depression-Focused Psychotherapy	Pharmacotherapy in Combination With Depression-Focused Psychotherapy	Electroconvulsive Therapy
Mild to Moderate	Yes	Yes	May be useful for patients with psycho-social or interpersonal problems, intrapsychic conflict, or co-occurring Axis II disorder	Yes, for certain patients
Severe Without Psychotic Features	Yes	No	Yes	Yes
Severe With Psychotic Features	Yes, provide both antidepressant and antipsychotic medication	No	Yes, provide both antidepressant and antipsychotic medication	Yes

FIGURE 1. Recommended Modalities for Acute Phase Treatment of Major Depressive Disorder

26

2010



PRACTICE GUIDELINE FOR THE
Treatment of Patients With Major Depressive Disorder
Third Edition

"If a patient wishes to try exercise... there is little to argue against it..."

If a patient with mild depression wishes to try exercise alone for several weeks as a first intervention, there is little to argue against it (Section II.A.10), provided the patient is sufficiently monitored for an abrupt worsening of mood or adverse physical effects (e.g., ischemia or musculoskeletal symptoms). The dose of exercise and adherence to an exer-

AMERICAN PSYCHIATRIC ASSOCIATION

27

Journal of Evaluation in Clinical Practice 19 (2013) 674–681

Conflicts of interest and the quality of recommendations in clinical guidelines†

Lisa Cosgrove, PhD[1,2] Harold J. Bursztajn, MD[4] Deborah R. Erlich, MD, MmedEd[5], Emily E. Wheeler, MS[3] and Allen F. Shaughnessy, PharmD, MmedEd[6]

Financial ties to industry were disclosed by all members (100%) of the guideline development committee with members reporting a mean 20.5 relationships (range 9–33). The majority of the committee participated on pharmaceutical companies' speakers' bureaus.

Dr. Thase reports that he provided scientific consultation to AstraZeneca, Bristol-Myers Squibb, Eli Lilly & Company, Forest Pharmaceuticals, Inc., Gerson Lehman Group, GlaxoSmithKline, Guidepoint Global, H. Lundbeck A/S, MedAvante, Inc., Neuronetics, Inc., Novartis, Otsuka, Ortho-McNeil Pharmaceuticals, PamLab, L.L.C., Pfizer (formerly Wyeth-Ayerst Laboratories), Schering-Plough (formerly Organon), Shire U.S., Inc., Supernus Pharmaceuticals, Takeda (Lundbeck), and Transcept Pharmaceuticals. He was a member of the speakers bureaus for [illegible] Company, GlaxoSmithKline, the National Institute of Mental Health, the Agency for Healthcare Research and Quality, and Sepracor, Inc. He had equity holdings in MedAvante, Inc., and received royalty income from American Psychiatric Publishing, Inc., Guilford Publications, Herald House, Oxford University Press, and W.W. Norton and Company. His wife was employed as the group scientific director for Embryon (formerly Advogent), which does business with Bristol-Myers Squibb and Pfizer/Wyeth.

28

Journal of Evaluation in Clinical Practice 19 (2013) 674–681

Conflicts of interest and the quality of recommendations in clinical guidelines†

Lisa Cosgrove, PhD[1,2] Harold J. Bursztajn, MD[4] Deborah R. Erlich, MD, MmedEd[5], Emily E. Wheeler, MS[3] and Allen F. Shaughnessy, PharmD, MmedEd[6]

recommendations. Fewer than half (44.4%) of the studies supporting the recommendations met criteria for high quality. Over one-third (34.2%) of the cited research did not study outpatients with major depressive disorder, and 17.2% did not measure clinically relevant results. One-fifth (19.7%) of the references were not congruent with the recommendations.

29

Ann Intern Med. 2016;164:350-359

Nonpharmacologic Versus Pharmacologic Treatment of Adult Patients With Major Depressive Disorder: A Clinical Practice Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Michael J. Barry, MD; and Devan Kansagara, MD, MCR, for the Clinical Guidelines Committee of the American College of Physicians

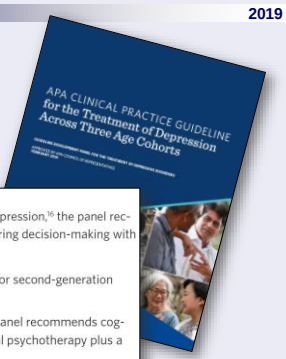
Recommendation: *ACP recommends that clinicians select between either cognitive behavioral therapy or second-generation antidepressants to treat patients with major depressive disorder after discussing treatment effects, adverse effect profiles, cost, accessibility, and preferences with the patient (Grade: strong recommendation, moderate-quality evidence).*

ACP American College of Physicians®
Leading Internal Medicine, Improving Lives

30

2019

AMERICAN PSYCHOLOGICAL ASSOCIATION



Psychotherapy and Pharmacotherapy

For initial treatment of adult patients with depression,[16] the panel recommends the following in the context of sharing decision-making with the patient when considering options:

1. That clinicians offer either psychotherapy or second-generation antidepressant.[17]
2. If considering combined treatment, the panel recommends cognitive-behavioral therapy or interpersonal psychotherapy plus a second-generation antidepressant.

31

Journal of Affective Disorders 147 (2013) 94–100

Treatment preferences in patients with first episode depression

Janie Houle [a,*], Benjamin Villaggi [a], Marie-Dominique Beaulieu [b], François Lespérance [c], Gilles Rondeau [d], Jean Lambert [c]

Antidepressants prescribed to **91%** of patients with first-episode depression

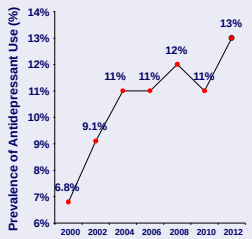
Characteristics	*n* (%)
Current treatment	
Antidepressants only	50 (56.8)
Psychotherapy only	2 (2.3)
Both treatments	30 (34.1)
None	6 (6.8)

32

JAMA. 2015;314(17):1818-1831

Trends in Prescription Drug Use Among Adults in the United States From 1999-2012

Elizabeth D. Kantor, PhD, MPH; Colin D. Rehm, PhD, MPH; Jennifer S. Haas, MD, MSc; Andrew T. Chan, MD, MPH; Edward L. Giovannucci, MD, ScD



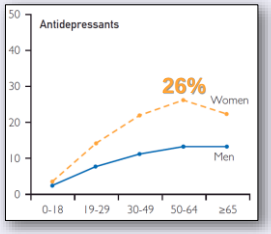
In 2012…	
Antihypertensives	27%
Antihyperlipidemics	18%
Antidepressants	13%

33

Mayo Clin Proc. 2013;88(7):697-707

Age and Sex Patterns of Drug Prescribing in a Defined American Population

Wenjun Zhong, PhD; Hilal Maradit-Kremers, MD, MSc; Jennifer L. St. Sauver, PhD, MPH; Barbara P. Yawn, MD, MSc; Jon O. Ebbert, MD; Véronique L. Roger, MD, MPH; Debra J. Jacobson, MS; Michaela E. McGree, BS; Scott M. Brue, BS; and Walter A. Rocca, MD, MPH

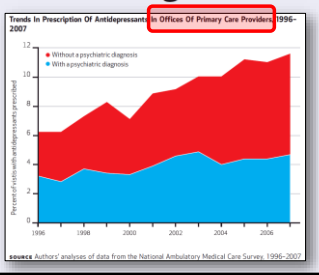


34

HEALTH AFFAIRS AUGUST 2011 30:8

By Ramin Mojtabai and Mark Olfson

Proportion Of Antidepressants Prescribed Without A Psychiatric Diagnosis Is Growing



35

Arch Gen Psychiatry. 2009;66(8):848-856

National Patterns in Antidepressant Medication Treatment

Mark Olfson, MD, MPH; Steven C. Marcus, PhD

Table 3. Clinical Characteristics of Persons Treated With Antidepressants in the United States, 1996 and 2005

Characteristics	Percentage (95% CI) MEPS 1996 (n = 1029)	MEPS 2005 (n = 2602)
Selected treated conditions		
Depression	26.25 (26.30-32.39)	26.85 (24.98-28.81)
Bipolar disorder	1.81 (1.09-3.01)	3.25 (2.49-4.23)
Anxiety	8.55 (6.92-10.52)	14.14 (12.70-15.71)
Adjustment	2.20 (1.46-3.29)	3.34 (2.58-4.30)
Headache	8.82 (7.04-11.01)	5.46 (4.52-6.58)
Back pain	12.95 (10.83-15.41)	15.17 (13.68-16.80)
Neuropathy	3.77 (2.87-5.37)	3.99 (3.25-4.88)
Fatigue	2.47 (1.60-3.81)	1.39 (0.93-2.08)
Sleep disorder	3.77 (2.87-5.37)	5.34 (4.43-6.43)
Mental health status		
Excellent to good	74.84 (71.13-78.23)	78.97 (76.97-80.85)
Fair to poor	25.16 (21.77-28.87)	19.15 (23.04-14.13)

36

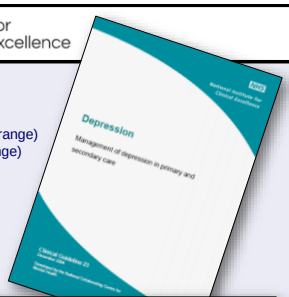
So, how good are the treatments?

37

NICE National Institute for Health and Care Excellence

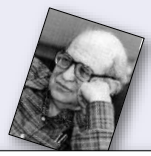
3 points on the HRSD (out of 0-52 range)
3 points on the BDI (out of 0-63 range)

or ***d* = 0.50** standard deviations

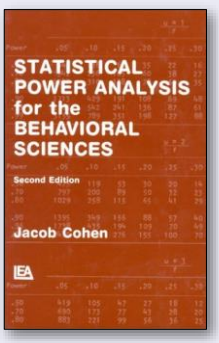


For continuous outcomes for which an SMD was calculated (for example, when data from different versions of a scale are combined), an effect size of ~0.5 (a 'medium' effect size; Cohen, 1988) or higher was considered clinically significant. Where a WMD was calculated, a between group difference of at least three points (two points for treatment-resistant depression) was considered clinically significant for both BDI and HRSD.

38



small: **d** = .20,
medium: **d** = .50,
large: **d** = .80.



39

JAMA Psychiatry. 2020;77(7):694-702

Psychotherapy for Depression Across Different Age Groups: A Systematic Review and Meta-analysis

Pim Cuijpers, PhD; Eirini Karyotaki, PhD; Dikla Eckshtain, PhD; Mei Yi Ng, PhD; Katherine A. Corteselli, MA; Hisashi Noma, PhD; Soledad Quero, PhD; John R. Weisz, PhD

Table 1. Comparison of Effect Sizes of Studies of Psychotherapies Compared With Control Groups and Across Age Groups

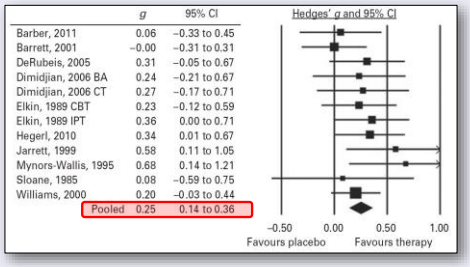
Comparisons	No. of Studies	g (95% CI)	I^2 (95% CI)
All comparisons	453	0.75 (0.67-0.82)	80 (78-82)

41

Psychological Medicine (2014), 44, 685–695

Comparison of psychotherapies for adult depression to pill placebo control groups: a meta-analysis

P. Cuijpers[1,2*], E. H. Turner[3,4], D. C. Mohr[5], S. G. Hofmann[6], G. Andersson[7,8], M. Berking[9] and J. Coyne[10]



42

Annals of General Psychiatry 2013, 12:26

No role for initial severity on the efficacy of antidepressants: results of a multi-meta-analy

Konstantinos N Fountoulakis[1*], Areti Angeliki Veroniki[2], Melina Siamouli[1] and Hans-Jürgen M

The use of SMD in a Bayesian RE [illegible]egression model suggests that the standardised [illegible] size of anti-depressants relative to placebo [illegible] (0.27–0.42), and there is no significant rol[illegible] the initial severity of depression. The most [illegible]e raw HDRS change score is 2.82 (2.21–3.4[illegible]ending above 3. Our analysis

The results reported here conclude the debate on the efficacy of antidepressants

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Annals of General Psychiatry 2013, 12:26

No role for initial severity on the efficacy of antidepressants: results of a multi-meta-analysis

Konstantinos N Fountoulakis[1*], Areti Angeliki Veroniki[2], Melina Siamouli[1] and Hans-Jürgen Möller[3]

Competing interests

KNF has received support concerning trave[illegible] from various pharmaceutical companies in order to participate [illegible] congresses. He has also received honoraria for lectures from Astra-Zeneca, Janssen-Cilag, Eli-Lilly and a research grant from Pfizer Foundation. MS has received support concerning travel and accommodation expenses from various pharmaceutical companies. HJM has received grants or is a consultant for and on the speakership bureaus of AstraZeneca, Bristol-Myers Squibb, Eisai, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, Merck, Novartis, Organon, Pfizer, Sanofi-Aventis, Sepracor, Servier and Wyeth. AAV has

4

18

44

Lancet 2018; 391: 1357-66

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

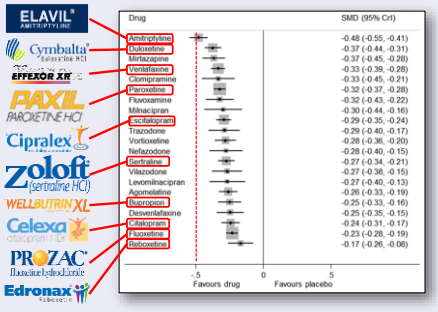
Andrea Cipriani, Toshi A Furukawa*, Georgia Salanti*, Anna Chaimani, Lauren Z Atkinson, Yusuke Ogawa, Stefan Leucht, Henricus G Ruhe, Erick H Turner, Julian P T Higgins, Matthias Egger, Nozomi Takeshima, Yu Hayasaka, Hissei Imai, Kiyomi Shinohara, Aran Tajika, John P A Ioannidis, John R Geddes

The relative efficacy of antidepressants compared with placebo is also shown for remission (appendix pp 152, 153). The random-effects summary SMD for all antidepressants was 0·30 (95% CrI 0·26–0·34; p<0·0001; appendix pp 150, 151). In terms of dropouts due to

45

Lancet 2018; 391: 1357-66

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis



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BBC NEWS

Anti-depressants: Major study finds they work

By Alex Therrien
Health reporter, BBC News

22 February 2018

Scientists say they have settled one of medicine's biggest debates after a huge study found that anti-depressants work.

Lead researcher Dr Andrea Cipriani, from the University of Oxford, told the BBC: "This study is the final answer to a long-standing controversy about whether anti-depressants work for depression.

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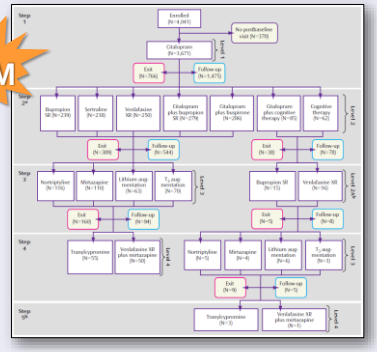
STAR*D
Sequenced Treatment Alternatives to Relieve Depression

$35M



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(*Psychiatric Services* 60:1439–1445, 2009)

What Did STAR*D Teach Us? Results From a Large-Scale, Practical, Clinical Trial for Patients With Depression

Bradley N. Gaynes, M.D., M.P.H.
Diane Warden, Ph.D., M.B.A.
Madhukar H. Trivedi, M.D.
Stephen R. Wisniewski, Ph.D.
Maurizio Fava, M.D.
A. John Rush, M.D.

Celexa citalopram HBr

STAR*D results
Level 1 outcomes
A total of 2,576 individuals with analyzable data completed level 1 treatment. Measurement-based care was feasible and led to an average citalopram dosage of greater than 40 mg per day, indicating that high-quality care was delivered in these real-world settings. Remission rates were 27% as measured by HAM-D and 33% as measured by QIDS-SR, and response rates were 47% as measured by QIDS-SR. For those whose symptoms remitted, the mean time to re-

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NIH National Institute of Mental Health

Questions and Answers about the NIMH Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study — All Medication Levels

November 2006

In conclusion, about half of participants in the STAR*D study became symptom-free after two treatment levels. Over the course of all four treatment levels, almost 70 percent of those who did not withdraw from the study became symptom-free. However, the rate

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CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 75 • NUMBER 1 JANUARY 2008

The STAR*D study: Treating depression in the real world

BRADLEY N. GAYNES, MD, MPH*
Associate Professor of Psychiatry, University of North Carolina School of Medicine; Investigator, Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study

A. JOHN RUSH, MD*
University of Texas Southwestern Medical Center at Dallas; Professor of Clinical Sciences and Psychiatry; Principal Investigator, STAR*D study

MADHUKAR H. TRIVEDI, MD*
University of Texas Southwestern Medical Center at Dallas; Professor of Psychiatry; National Coordinating Center, STAR*D study

STEPHEN R. WISNIEWSKI, PhD*
University of Pittsburgh School of Medicine; Associate Professor of Epidemiology; Data Coordinating Center, STAR*D study

DONALD SPENCER, MD, MBA*
University of North Carolina School of Medicine; Professor of Family Medicine; Investigator, STAR*D study

MAURIZIO FAVA, MD*
Massachusetts General Hospital, Boston; Professor of Psychiatry; Investigator, STAR*D study

- For patients who present with major depressive disorder, STAR*D suggests that with persistence and aggressive yet feasible care, there is hope: after one round, approximately 30% will have a remission; after two rounds, 50%; after three rounds, 60%; and after four rounds, 70%.

The theoretical cumulative remission rate after four acute treatment steps was 67%.

51

Can J Psychiatry 2015;60(1):9–13

The STAR*D Trial: It Is Time to Reexamine the Clinical Beliefs That Guide the Treatment of Major Depression

H Edmund Pigott, PhD[1]

treatment effects is even paltrier. Only 2.7% of patients had a QIDS-SR determined remission after up to 4 rounds of AD drug care and neither relapsed nor dropped out as evidenced by taking at least 1 of the months 10-to-12 QIDS-SR telephonic assessments and not scoring as having relapsed in any of the 12 monthly administered assessments.

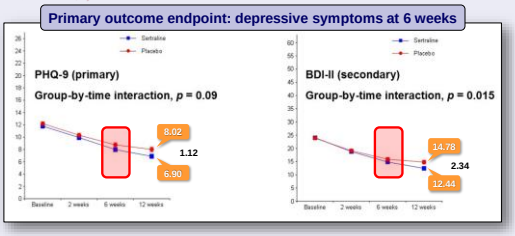
52

Lancet Psychiatry 2019; 6: 903-14

The clinical effectiveness of sertraline in primary care and the role of depression severity and duration (PANDA): a pragmatic, double-blind, placebo-controlled randomised trial

Gemma Lewis, Larisa Duffy, Anthony Ades, Rebekah Amos, Ricardo Araya, Sally Brabyn, Katherine S Button, Rachel Churchill, Catherine Derrick, Christopher Dowrick, Simon Gilbody, Christopher Fawsitt, William Hollingworth, Vivien Jones, Tony Kendrick, David Kessler, Daphne Kounali, Naila Khan, Paul Lanham, Jodi Pervin, Tim J Peters, Derek Riozzie, George Salaminios, Laura Thomas, Nicky J Welton, Nicola Wiles, Rebecca Woodhouse, Glyn Lewis

Primary outcome endpoint: depressive symptoms at 6 weeks



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BBC NEWS

Sertraline: Antidepressant works 'by reducing anxiety symptoms first'

20 September 2019

A commonly-prescribed antidepressant reduces anxiety first and has a smaller effect on depressive symptoms weeks later, a study suggests.

Researchers at University College London said it made people feel better but worked in unexpected ways.

Their trial involved 653 UK patients, half of whom were given sertraline and the other half a placebo (dummy pill).

Psychiatrists say the findings are reassuring for doctors and patients, confirming the benefits of treatment.

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Antidepressants: Examples of Possible Side Effects

Relatively minor; usually short-lived

- Diarrhea
- Dizziness
- Dry mouth
- Headaches
- Nausea
- Sweating
- Tremors

More serious. Can be dangerous. May need to switch drugs if they persist.

- Drowsiness or confusion
- Feeling of panic or dread
- Increased thoughts of suicide
- Insomnia
- Loss of libido, difficulty achieving erections, inability to reach orgasm
- Nervousness and agitation
- Weight gain

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WARNING: Suicidality and Antidepressant Drugs

See full prescribing information for complete boxed warning.

- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Cymbalta is not approved for use in pediatric patients (5.1).**

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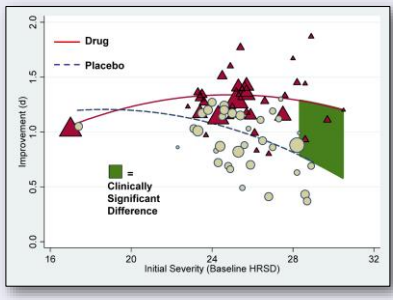
So, what about exercise?

57

PLoS MEDICINE 2008 | Volume 5 | Issue 2 | e45

Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration

Irving Kirsch[1*], Brett J. Deacon[2], Tania B. Huedo-Medina[3], Alan Scoboria[4], Thomas J. Moore[5], Blair T. Johnson[3]



Irving Kirsch

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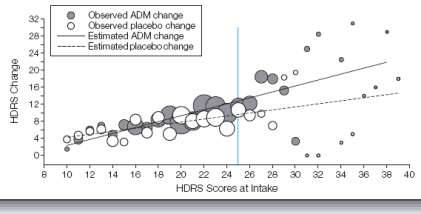
JAMA. 2010;303(1):47-53

Antidepressant Drug Effects and Depression Severity

A Patient-Level Meta-analysis

Jay C. Fournier, MA
Robert J. DeRubeis, PhD
Steven D. Hollon, PhD
Sona Dimidjian, PhD
Jay D. Amsterdam, MD
Richard C. Shelton, MD
Jan Fawcett, MD

Figure 2. Observed and Estimated Change in HDRS Scores Following Treatment With ADM and Placebo



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N Engl J Med 2008;358:252-60.

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.

Published literature: 94% of the trials were positive

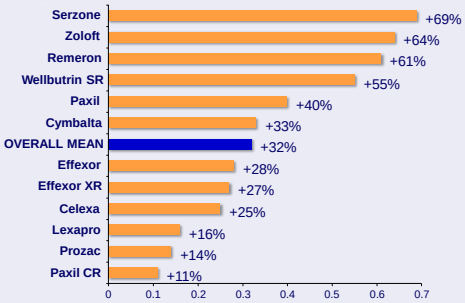
FDA database: 51% of the trials were positive

...in a way that, in our opinion, conveyed a positive outcome (11 ... 5). According to the published literature, it appeared that 94% of the trials conducted were positive. By contrast, the FDA analysis showed that 51% were positive. Separate meta-analyses of the FDA and journal data sets showed that the increase in effect size ranged from 11 to 69% for individual drugs and was 32% overall.

60

N Engl J Med 2008;358:252-60.

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy



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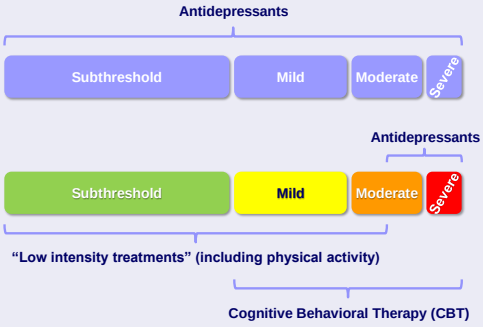
Stepped (Collaborative) Care Approach



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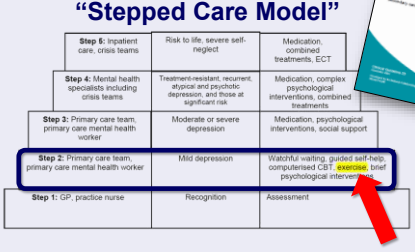
NICE National Institute for Health and Care Excellence

"Stepped Care Model"



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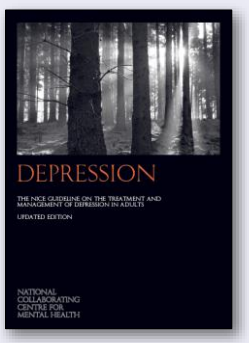
NICE National Institute for Health and Care Excellence



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NICE National Institute for Health and Care Excellence

7.5 RECOMMENDATIONS

Low-intensity psychosocial interventions

7.5.1.1 For people with persistent subthreshold depressive symptoms or mild to moderate depression, consider offering one or more of the following interventions, guided by the person's preference:

- individual guided self-help based on the principles of cognitive behavioural therapy (CBT)
- computerised cognitive behavioural therapy (CCBT)[52]
- a structured group physical activity programme.

7.5.1.4 Physical activity programmes for people with persistent subthreshold depressive symptoms or mild to moderate depression should:

- be delivered in groups with support from a competent practitioner
- consist typically of three sessions per week of moderate duration (45 minutes to 1 hour) over 10 to 14 weeks (average 12 weeks).

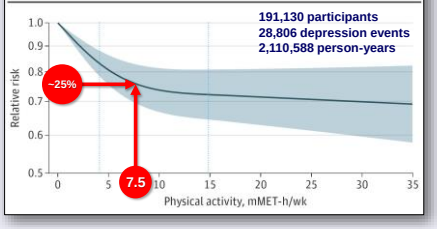
65

JAMA Psychiatry. 2022;79(6):550-559

Association Between Physical Activity and Risk of Depression
A Systematic Review and Meta-analysis

Matthew Pearce, PhD; Leandro Garcia, PhD; Ali Abbas, PhD; Tessa Strain, PhD; Felipe Barreto Schuch, PhD; Rajna Golubic, PhD; Paul Kelly, PhD; Saad Khan, MB,BChir; Mrudula Utukuri, MB,BChir; Yvonne Laird, PhD; Alexander Mok, PhD; Andrea Smith, PhD; Marko Tainio, PhD; Søren Brage, PhD; James Woodcock, PhD

Figure 1. Association Between Physical Activity and Incidence of Depression



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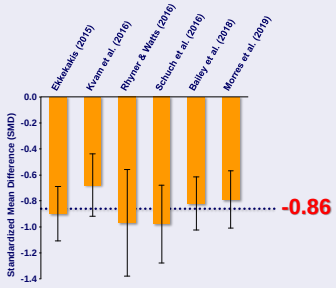
Meta-Analyses: Effects of Exercise on Depression



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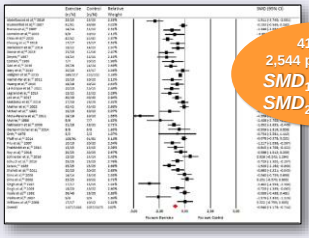
Br J Sports Med 2023

Exercise as medicine for depressive symptoms? A systematic review and meta-analysis with meta-regression

Andreas Heissel ,[1] Darlene Heinen ,[1] Luisa Leonie Brokmeier ,[1] Nora Skarabis,[1] Maria Kangas ,[2] Davy Vancampfort ,[3] Brendon Stubbs ,[4] Joseph Firth ,[5] Philip B Ward ,[6] Simon Rosenbaum ,[7] Mats Hallgren ,[8] Felipe Schuch [9,10,11]



41 RCTs
2,544 participants
SMD_1 = -0.946
SMD_2 = -0.717

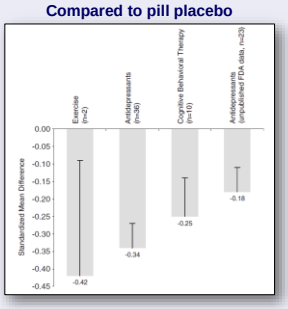
68

General Hospital Psychiatry 49 (2017) A1–A5

Exercise as antidepressant treatment: Time for the transition from trials to clinic?

Panteleimon Ekkekakis[a,*], Martino Belvederi Murri[b]

Compared to pill placebo



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Australian and New Zealand Journal of Psychiatry 2007; 41:32–37

Judged effectiveness of differing antidepressant strategies by those with clinical depression

Gordon Parker, Joanna Crawford

Survey of 2,692 respondents with a clinically diagnosed depressive episode

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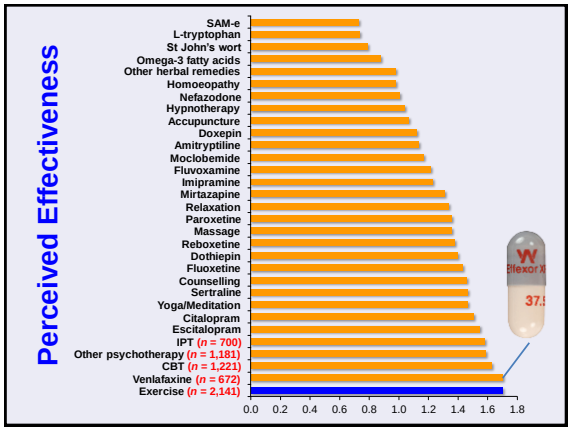

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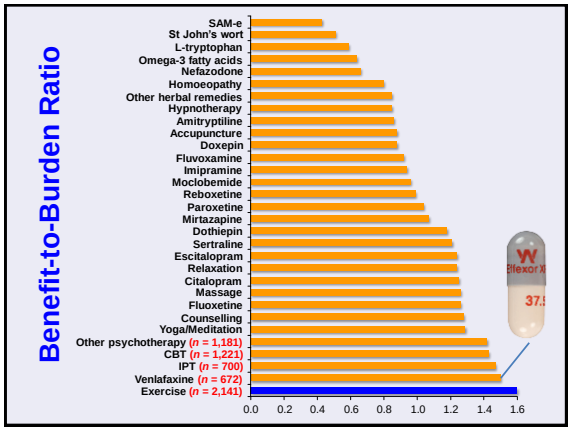

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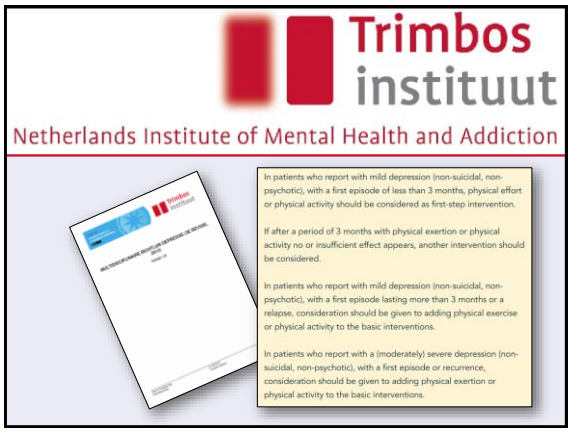

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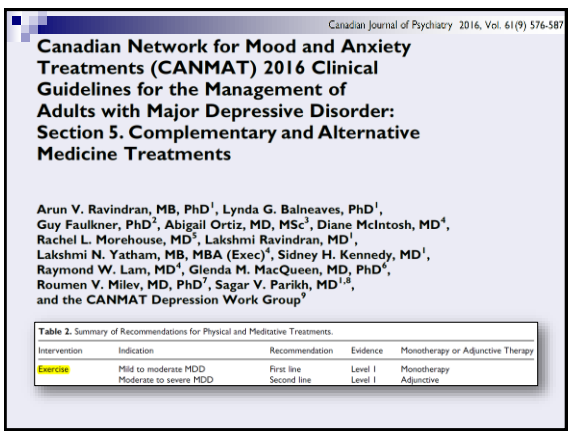

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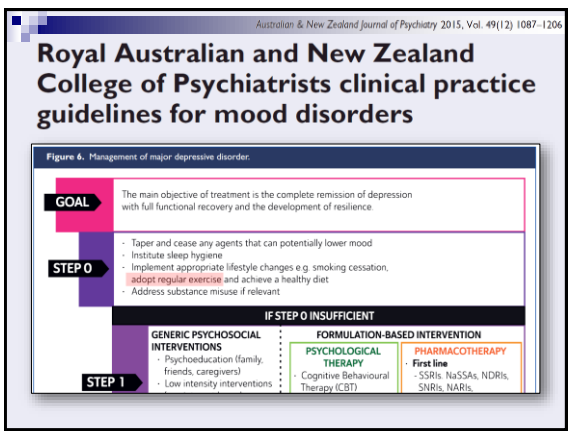

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European Psychiatry 54 (2018) 124–144

EPA guidance on physical activity as a treatment for severe mental illness: a meta-review of the evidence and Position Statement from the European Psychiatric Association (EPA), supported by the International Organization of Physical Therapists in Mental Health (IOPTMH)

Brendon Stubbs[a,b,*], Davy Vancampfort[c], Mats Hallgren[d], Joseph Firth[e,f], Nicola Veronese[g], Marco Solmi[h], Serge Brand[i,j,k], Joachim Cordes[l], Berend Malchow[m], Markus Gerber[i], Andrea Schmitt[m,n], Christoph U. Correll[o,p,q], Marc De Hert[r], Fiona Gaughran[a,b], Frank Schneider[s], Florence Kinnafick[t], Peter Falkai[m], Hans-Jürgen Möller[m], Kai G. Kahl[u]

recommendations. For MDD, consistent evidence indicated that PA can improve depressive symptoms versus control conditions, with effects comparable to those of antidepressants and psychotherapy. PA can also improve cardiorespiratory fitness and quality of life in people with MDD, although the impact on physical health outcomes was limited. There were no differences in adverse events versus control conditions. For MDD, larger effect sizes were seen when PA was delivered at moderate-vigorous intensity and supervised by an exercise specialist. For schizophrenia-spectrum disorders, evidence

EPA European Psychiatric Association

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79

BMC Family Practice 2014, 15:5

Stepped care for depression is easy to recommend, but harder to implement: results of an explorative study within primary care in the Netherlands

Marleen LM Hermens[1*], Anna Muntingh[1,2], Gerdien Franx[1], Peter T van Splunteren[1] and Jasper Nuyen[1]

lifestyle advice (e.g. on healthy diet and exercise). Patients were seldom referred to group courses or to running therapy. E-health interventions were provided sparsely by both the GPs and the

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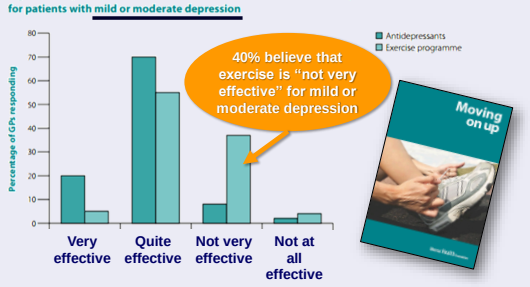
mental health foundation

Figure 1: GP perceptions of the effectiveness of exercise and antidepressants for patients with mild or moderate depression



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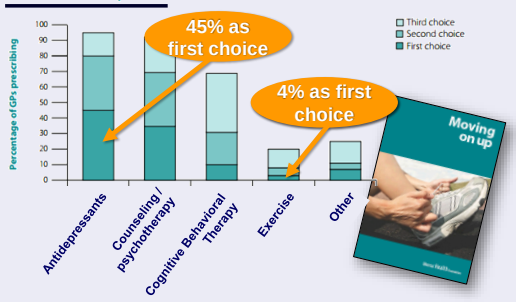
mental health foundation

Figure 2: GP preferred choices of treatment for patients with mild or moderate depression



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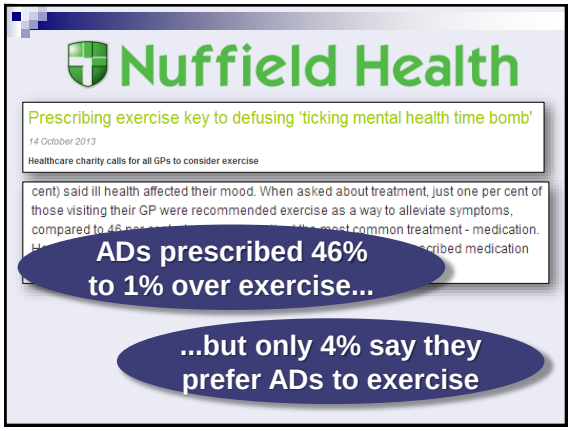
Nuffield Health
Prescribing exercise key to defusing 'ticking mental health time bomb'
14 October 2013
Healthcare charity calls for all GPs to consider exercise
cent) said ill health affected their mood. When asked about treatment, just one per cent of those visiting their GP were recommended exercise as a way to alleviate symptoms, compared to 46 per
most common treatment - medication.
scribed medication
ADs prescribed 46% to 1% over exercise...
...but only 4% say they prefer ADs to exercise

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Thank you!
http://Ekkekakis.org
@Ekkekakis
MICHIGAN STATE UNIVERSITY

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