A multidisciplinary intervention to improve mood, postural stability, and dyspnea among elderly with major depression: the He.s.i.o.d. study (Hexameter Study In Older Depressed)

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The Hesiod Study group

Late Life Major Depression: Facts



Heterogeneous clinical picture: depressed mood, lack of initiative, neurovegetative symptoms (e.g. sleep and appetite disturbances), cognitive dysfunction

Is common: In primary care practices, 15.1% to 35.9% of patients over 65 years of age have subthreshold depression and 20% have Major Depressive Disorder

Has negative outcomes: Causes disability and worsens quality of life; complicates the course of associated physical illnesses and increases mortality; high risk of suicide

Tendancy for chronicity: 50% of patients relapse within 18 months

Is expensive: Direct costs around 1500 euros (~US \$1700) per person per year

Is still under-diagnosed and undertreated

Is difficult to treat: Low remission rates (28-44%) with first-line anti-depressants

Alexopoulos, *Lancet*, 2008; Meeks et al., JAD, 2011; Luppa et al, 2008; Roose and Schatzberg, 2005; Pompili et al, 2008; Mueller, et al., 2004

Late Life Major Depression: other facts



Not just in the mind:

cerebrovascular damage, reduced neuroplasticity, autonomic dysregulation, HPA axis hyperactivity, inflammatory imbalances, worse prognosis of associated medical conditions; higher mortality

<u>**Risk of falls and Fear of falling:**</u> depression is associated with fear of falling, objective postural instability and increased risk of falls

Dyspnea: symptoms of anxiety (OR 3.53 (1.03-12.1)) and depression (OR 12.2 (3.97-37.5)) are prospectively associated with developing dyspnea

<u>Anxiety and cognitive deficit</u> as common residual symptoms after antidepressant treatment

Belvederi Murri et al., PNEI, 2014 Rosengren et al., Lancet 2004; Van der Kooy et al., Int J Ger Psych 2007; Carney et al, 2009, Taylor et al, 2010; Amore et al., Stress 2015; Neuman et al., Respiratory Medicine (2006); Denkinger et al., 2015, Am J Ger Psych; Deshpande et al., Am J Phys Med Rehabil. 2008; Stubbs et al., Int Psychoger 2016; Alexopoulos and Morimoto et al., Ann N Y Acad Sci 2015

Physical Exercise as a Treatment for Depression

- Tackles most biological correlates of depression (biological plausibility):
 - Increases brain monoamines, favors neuroplasticity, reduces stress response and inflammatory markers
 - Improves mood, sleep, and neurocognitive functions ("runner's high")
- Already recommended by several guidelines as a treatment option for mild-to-moderate depression
- Evidence of efficacy among elderly (effect size: 0.6 reducing depressive symptoms' severity)





Christie et al., Neuromolecular Med. 2008; Ma et al., Neurosci Bull. 2008; Archer et al., CNS Neurol Disord Drug Targets. 2014; Ekkekakis P., 2015; Bridle et al., Brit J Psych, 2012; Rhyner and Watts 2016

<u>SEEDS study: main findings</u> <u>Safety and Efficacy of Exercise for Depression in Seniors</u>

- Compared standard antidepressant therapy (sertraline) with antidepressant plus physical exercise (S+EX) in 121 older depressed individuals (mean age 75)
- S+EX was safe! No major side effects
- S+EX led to greater improvements of **depression** (symptom severity and remission rates) because of greater effects on **affective symptoms** ("core" depressive symptoms).
- Aerobic exercise was associated with greater improvement of disability and cognitive domains
- S+EX was associated with greater improvements of **cardiovascular risk** (Heart Rate Variability, index of autonomic control of the heart)



Belvederi Murri et al., Br J Psych 2015; Toni et al., Am J Geriatr Psychiatry. 2016; Neviani et al., Int Psychogeriatr. 2017; Zanetidou et al., J Am Geriatr

SEEDS study: main findings <u>Safety and Efficacy of Exercise for Depression in Seniors</u>

- HOWEVER...
 - <u>Less effective among individuals with higher baseline</u> <u>anxiety</u>
 - Unknown effects on dyspnea
 - Unknown effects on postural stability and risk of falls



Belvederi Murri et al., Br J Psych 2015; Toni et al., Am J Geriatr Psychiatry. 2016; Neviani et al., Int Psychogeriatr. 2017; Zanetidou et al., J Am Geriatr

He.s.i.o.d. study Hexameter Study In Older Depressed



- 1) recitation of hexameter verse
- 2) controlled breathing
- 3) spontaneous breathing





Fig. 2. A: increase of the phase difference $\phi_{\text{resp}}(t_i) - \phi_{\text{heart}}(t_i)$ during baseline measurement S1 denotes a desynchronized state between the heart rate time series and the low-frequency component of the nasal/oral time series ($\gamma = 0.14$). B: cardiorespiratory synchronization during hexameter recitation: the phase difference shows plateaus at different levels and an obvious maximum in the distribution of $\Psi(t_i)$, which is also reflected by $\gamma = 0.78$.

Cysarz et al., Am J Physiol Heart Circ Physiol, 2004

Intervention at study: BREATHING/POSTURAL EXERCISES PLUS ANTIDEPRESSANT DRUG (HESIOD)



The intervention consists in breathing and postural exercises, under trained staff supervision (professional actor and graduate in Sport Science). Respiratory exercises consist in respiratory muscles training, forced expiration, thoracic expansion techniques, during the rhythmic recitation of hexameter poetry. Hexameter recitation has known positive effects on cardio-respiratory synchronization (Cysarz et al., 2004). Postural exercises involve upper and lower limb strengthening, motor coordination and education. The one-hour sessions are held weekly in groups of 5-10 subjects, for 24 weeks.

Comparison group: GROUP READING PLUS ANTIDEPRESSANT DRUGS



The intervention consists in weekly reading group under the supervision of a trained psychiatrist. Participants are asked to read, comment and discuss short pleasurable stories and fables that have been written by students. The one-hour sessions are held weekly in groups of 5-10 subjects, for 24 weeks.

Hesiod Assessments



OUTCOMES MADRS Montgomery-Asberg Depression Rating Scale depression and anxiety severity (total and anxiety factor scores)

FES-I Falls Efficacy Scale, fear of falling
MOCA cognitive assessment
Functional Status & Dyspnea Questionnaire-Modified (PFSDQ-M)
Timed Up and Go test (TUG). A smartphone-based system developed by mHealth
Technologies to assess postural stability (Palmerini et al., 2013)
baseline, 12 and 24 weeks



Hesiod Results

	Control (n=29)	HESIOD (n=26)	statistics
age	74.7 ±7.2	73.5 ±7.8	P=0.52
Female, %	69.0	76.9	P=0.51
BMI	26.6 ±4.3	26.0 ±3.2	P=0.57
CIRS severity	1.47 ±0.5	1.47 ±0.4	P=0.98
CIRS comorbidity	1.80 ±2.3	1.96 ±2.3	P=0.79
MOCA total	21.3 ±6.2	23.5 ±5.7	P=0.17
MADRS total	25.0 ±8.0	22.7 ±9.7	P=0.35
Anxiety subscale	2.15 ±0.75	1.87 ±0.81	P=0.19
Fear of falling	26.1 ±9.8	22.5 ±5.9	P=0.12
Dyspnea	0.75 ±1.23	0.76 ±0.97	P=0.97

Hesiod Results

TUG factors at baseline (Hesiod and control group)



	MADRS_ANX	FES	dyspnea
t0_MADRS_ANX	1	,252	,303*
		,064	,026
T0_FES_TOT	,252	1	,810**
	,064		,000



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Intervention
I control
I HESIOD
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At 3 months difference between MADRS total score p=0.01; at 6 months difference (depression severity) p=0.046 *



At 3 months difference between MADRS ANXIETY SUBSCALE p=0.07 ; at 6 months difference (depression severity) p=0.08



OF FALLING (FES-I) questionnaire p=0.03 ; at 6 months difference (depression severity) p=0.047

No significant difference in DYSPNEA questionnaire scores



Conclusions

- Late life depression a complex disorder with negative physical consequences
- Adding physical Exercise to antidepressants is effective against various dimensions of late life depression
- However, less effective against anxiety and unknown effects on fear of falling, postural stability, dyspnea
- Hexameter recitation and postural rehabilitation is more effective than active control against depression&anxiety
- Prelim results suggest it may also improve fear of falling and postural stability

Thank You. Grazie Mille.

Hesiod Acknowledgements

Università degli Studi di Modena e Reggio Emilia

Prof. Mirco Neri; Dr.ssa Francesca Neviani; Dr. Ferdinando Tripi; Dr. Mannina; Sandro Zoboli, dr. Niccolò Colombini, dr.ssa Silvia Ferrari, dr. Federzoni Guido

Dip. di Salute Mentale, Psichiatria di

Consultazione Dr.ssa Stamatula Zanetidou; Dr. Roberto Senaldi; Dr.ssa Serena Ferrara; Dr. Enrico Tam; Giuliana Tola; Lorenzo De Bei

Istituto di Psichiatria, Università di Bologna Prof. Marco Menchetti; Dr.ssa Claudia Luciano; dr.ssa Federica Casini, Roberto Rizzo; Davide Comastri

Dip. Di Neuroscienze, Università di Parma e Dip. Di Clinica Medica, Nefrologia e Scienze della Prevenzione Prof. Mario Amore; Dr. Aderville Cabassi; Prof. Cristina Montegano, Dr. Graziano Ceresini, Dr.ssa Arianna Montali, Dr.ssa Maria Lidia Gerra

Ospedale di S. Sebastiano di Correggio Dr. Giulio Toni; Gabriele Torcianti; Dr.ssa Morena Pellati, Prof. Massimo Piepoli, dr.ssa Veronica Barbanti Silva, dr.ssa Elena Francia





Primary Care Physicians, Bologna Dr. Luigi Bagnoli; Dr. Donato Zocchi; Dr. Giuliano Ermini; Dr. Piero Casarini; Dr. Carlo Spezia; Dr.ssa Monica Magagnoli; Dr.ssa Barbara Assirelli

Dip. Cure Primarie, AUSL Bologna Dr. Francesco Ripa di Meana, Angelo Fioritti, Dr.ssa Paola Argnani; Dr. Fausto Trevisani; Dr.ssa Maria L. Marcaccio; Dr.ssa Mara Morini

Dip. Di Fisiologia Umana, Università di Bologna Prof. Giovanni Zamboni; Prof. Pasquale Squatrito; Dr. Matteo Cerri; Dr. Alessandro Piras;

Dip. di Scienze Biomolecolari, Università degli Studi di Urbino Prof. Marco Bruno Luigi Rocchi

Dip. di Neuroscienze, Università di Genova Prof. Mario Amore, Dr. Martino Belvederi Murri, Dr. Mattia Masotti

Dip. Vari Dr. Giovanni De Girolamo, Dr. Danilo Di Diodoro, Dr. Giovanni Neri

Weill-Cornell Institute of Geriatric Psychiatry, Cornell University, New York Prof. George S. Alexopoulos

Center for Health Services Research in Primary Care and the Department of Family & Community Medicine , UC Davis Prof. Klea D. Bertakis, MD, MPH