

Psychiatric Centre Graz and Vienna), mobile social psychiatric care in old age (best practice-project SOPHA in Graz: Sozialpsychiatrische Hilfe im Alter - social psychiatric help in old age), day care centre for people with dementia and specialisation on age and dementia in all areas (geriatric psychiatrist, geriatric psychotherapists, in social work, psychology, care etc.).

All these measures may not be a cure but tertiary prevention in the best possible way. The daily routine in the GPZ shows that the counselling and the relief of the relatives can already bring an improvement and help the patient feel more relaxed, also cognitively. Not because dementia has 'got better' but because strain and stress may effectively be reduced, and so there can be literally 'more clarity'...

The aim of this workshop is to build a bridge between the pure somatic-drug-treated approach to dementia and the psychodynamic oriented, social psychiatric approach, and to raise awareness for our attitude by lively discussions and exchange of experience.

#### References:

1. Feil N, Altman R: *Validation theory and the myth of the therapeutic lie. American Journal of Alzheimer's Disease and Other Dementias 2004; 19:77-8*
2. Hirsch RD: *Socio- and psychotherapy in patients with Alzheimer disease. Zeitschrift für Gerontologie und Geriatrie 2001; 34:92-100*
3. Kasl-Godley J, Gatz M: *Psychosocial interventions for individuals with dementia: an integration of theory, therapy, and a clinical understanding of dementia. Clinical Psychology Review 2000; 20:755-82*
4. Patel B, Perera M, Pendleton J, Richman A, Majumdar B: *Psychosocial interventions for dementia: from evidence to practice. Advances in Psychiatric Treatment 2018; 24:340-349*
5. Psota G: *Social psychiatric aspects of dementia. Psychiatr Danub 2015; 27:432-438*
6. Wolf A, Leucht S, Pajonk FG: *Do antipsychotics lead to cognitive impairment in dementia? A meta-analysis of randomised placebo-controlled trials. European Archives of Psychiatry and Clinical Neuroscience 2017; 267:187-198*

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## PLACEBO AND NOCEBO PHENOMENA: A BIG CHALLENGE TO MODERN CLINICAL PSYCHIATRY

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Placebo and nocebo are fascinating and universal psyche-body or psychobiological as well as spiritual, social, and cultural phenomena, very important for treatment outcome in medicine in general, not only in psychiatry. As these very important and complex phenomena have been commonly viewed through reductionist lenses in hot debates and discusses, rather than in scientific dialogue, in the literature one can find many controversial definitions, misconceptions and myths about placebo and nocebo effects and responses. For example, many physicians still believe that placebo is just an unethical fraud, has no effect on physiological functions and only affects subjective aspects of illness and not objective measures of disease, helps only in imaginary, psychogenic or neurotic, but not in real, organic disorders. Claiming that is based on deceitful practice, the use of placebo should be minimized and avoided in scientific medicine and clinical psychiatry. Until recently nocebo was less known to majority of health care professionals and the data on it are still scarce. Serious analysis of placebo and nocebo responses may put into question the results of many commercially funded, randomized clinical drug trials which are the cornerstone of evidence based medicine in psychiatry. In medicine, placebo and nocebo phenomena are usually defined as positive or negative nonspecific psychological and physiological responses to inert substance or irrelevant procedure. In addition, a placebo procedure or substance represent an inert or officially nontherapeutic substance or irrelevant procedure, while placebo or nocebo response/effect is positive or negative reaction that follows administration of an inert substance or irrelevant treatment. However, placebo and nocebo phenomena are much more, they are genuine effects and responses that can more or less affect everyone and every kind of treatment. These phenomena have potential to powerfully improve or worsen mental or somatic symptoms without official or proven medical or psychotherapeutic intervention as well as during the standardized treatment. Placebo effects may be defined as positive psychophysiological or salutogenic responses that follow the administration of active and non-active substances/pills or procedures when coupled with affirmative narratives, faith and expectations about the treatment. In opposite way, nocebo effects may be viewed as pathogenic or pathopsychophysiological responses that follow the administration of active and non-active substances/pills or procedures when associated with negative, pessimistic or frightening narratives about the treatment. Placebo response seems to be associated with resilience and salutogenesis-related mechanisms that operate in the service of

wellness and health. On the other side, nocebo response may be associated with pathogenesis-related mind body processes which operate in the service of disease, illness and sickness.

At the end of the day, placebo and nocebo may represent the personal responses to any kind of treatment, so they are very important phenomena from the perspective of the person-centered medicine. Patients are always subjects who give sense and respond more or less actively to meanings that disease, illness and treatment have for them and their physicians. Inducing/eliciting placebo effects can be understood as a form of supplemental or complementary narrative therapy. Concept of narrative person-centered pharmacotherapy supports a shift from impersonal disease model and demoralizing prognostic skepticism towards optimism and personal recovery broadening treatment goals beyond symptom reduction and elimination to personal recovery. Patients always bring into treatment unique characteristics related to their personal life story, vulnerability, resilience and potential for personal growth as well as proneness to placebo or nocebo responsiveness. Disease has to be treated, but the needs of the suffering person have also to be met, helped with and healed. The close interconnectedness of the spirit, mind, brain, endocrine and immune systems suggests existence of an operating "self-aware healing system" of human beings which works silently in the background regulating and coordinating all living processes. Activation of this healing and resilience system is followed by the placebo response. Resilience is a protective collection of thoughts, actions and behavior which involves the one's positive attitude toward *restoration* (optimistic thinking, having faith in getting better), *the power to reconstruct* (ability to re-integrate overcoming difficulty, confidence to overcome difficulties) and *control one's disease* (coping skills, ability to control relapse prevention and illness, practicing health plan well), and *positive mutual interaction with supportive resource* (support from medical experts, from family members, friends and other people). Placebo & nocebo response may be related to one or more optimism-pessimism expectation-activated neuropsychophysiological systems or neuronal circuits, like reward-punishment system, novelty-seeking system, harm-avoidance system. Placebo reactions are positively, and nocebo reactions are inversely related to the reward system activity, as evidenced by measuring dopamine and endogenous release. Nocebo response may be associated with the punishment system activation. According to some opinions, dopamine signaling plays an important role in discrepancy between predicted and actual reward which may be the critical aspect for placebo or nocebo response. The serotonin system through its effects on mood and stress may relate to placebo or nocebo responses so that elevated serotonin activity stimulates the placebo response and counteract the nocebo response in pain syndromes and Parkinson's disease. The endogenous opioid system and cholecystokinin system are also important for placebo and nocebo responses, particularly for analgesia and hyperalgesia. The anterior cingulate cortex, an important anatomical component of the both dopaminergic and opioid systems, is reported to be activated during placebo analgesia, placebo anxiety relief and placebo mood improvement. The prefrontal cortex is related to many functions such as expectation generation, cognitive appraisal, memory retrieval and emotion modulation. A loss of prefrontal control is associated with a loss of placebo response. Mesolimbic and mesocortical modulation of stress and emotions may be also related to placebo or nocebo responses. The hypothalamic-pituitary-adrenal axis activity seems to be boosted by pessimistic expectancy, and is supposed to be a direct mediator of the nocebo response.

Despite the significant progress that placebo and nocebo research has made over recent decades, particularly in the neurobiology and psychodynamics, many questions and dilemmas still remain open. It seems that our better understanding of placebo and nocebo phenomena demands new models of the psyche-brain networks that simultaneously provide explanations of psychoneurobiological mechanisms and meaning, of symbols and their grounding, of context and its brain-psyche embodiment. The aim and purpose of this presentation is to give a transdisciplinary and integrative overview of the current research and understanding of the placebo and nocebo from the seven perspective (disease perspective, person-centered perspective, cognitive perspective, behavioral perspective, narrative perspective, spiritual perspective and systems perspective) as well as to provide some practical tips on how to manage placebo & nocebo phenomena in clinical practice for the well-being of patients.

#### References:

1. Jakovljevic M: *The placebo-nocebo response: Controversies and challenges from clinical and research perspective. European Neuropsychopharmacology* 2014a; 24:333-341
2. Jakovljevic M: *The placebo-nocebo response in patients with depression: do we need to reconsider our treatment approach and clinical trial designs? Psychiatr Danub* 2014b; 26:92-95
3. Jakovljevic M: *Person-centred psychopharmacotherapy: What is it? Each Patient is a unique, responsive and responsible subject. Psychiatr Danub* 2015; 27(suppl 1):28-33
4. Jakovljevic M & Abou-Salex MT: *Person Centered Psychopharmacotherapy. In Mezzich JE, Botbol M, Christodoulou GN, Cloninger CR & Salloum IM (eds): Person Centered Psychiatry, 235-245. Springer, 2016, 26*
5. Jakovljevic M: *Placebo and nocebo phenomena from the perspective of evidence-based and person centered medicine. Hospital Pharmacology* 2017; 4:512-520. ISSN 2334-9492 (Online)