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ETHICAL APPROACH TO PHARMACOTHERAPY OF COMORBID STATES

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SUMMARY

Ethics is an indispensable component of health care policy. Pharmacotherapy of comorbidity requires the use of a greater number of different drugs that have complex drug-drug interactions and drug-patient interactions which can cause various side-effects in the patient. The basic moral questions that justify the applied psychopharmacotherapy are the patient's welfare and preference, optimal relationship between risk and gain for the patient, and some include cost benefit as well.

Key words: *comorbidity – pharmacotherapy - ethics*

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Ethics in a wider health context

The concepts of defining health and illness are numerous and various. Approaches to this problem are biological and medical (molecular and holistic) on the one hand, sociological, psychological, ethnological, religious and philosophical on the other hand, and then there are economic, legal, hermeneutic and many other approaches. It is undeniable that the problems of health and illness, even when they are described in this way, can be studied only in the context of organization of the overall health system and health policy which are described in more detail below. Namely, the goals of health system are the following: promotion of health, prevention of illness, early detection and diagnosis, treatment of illness and rehabilitation. Through time and development of medical science and practice priorities among these goals were changing. Today emphasis is put on prevention of illness and promotion of health which are recognized as primary goals.

When talking about politics, whether it be national, supranational or the politics of the so called lower levels, what is primarily meant are the criteria and principles of decision making within a segment or field of activity (Adizes 1996).

Just like the other, the concept of health politics is based primarily on the existence of political decisions based on which resources are allocated, the level of equality in the allocation of resources and the participation of the community in attaining health. Health system is a comprehensive body of interactions of rights and obligations of the system holders, an individual, the community and health care on different levels. What actually functions in practice are different combinations of interactions of the above mentioned factors. Each of the subsystems within healthcare system has its goals and politics. The strategy of a successful realization of a goal is defined by the mission, i.e. the vision of that particular system (Courtney 2001, Scott et al. 1993, Green & Kreuter 1999, Džakula et al. 2007).

Ethics is an indispensable component of health care policy. It can be viewed from the perspective of metapolitics, megapolitics and specific politics. Ethics from the perspective of metapolitics represents ideals, values, general position in society such as comprehensiveness of health care system, interdisciplinarity in health care, etc. Ethics in the framework of megapolitics represents a platform that connects several general goals, such as WHO program "Health for all by the year 2000". Ethics in the framework of specific politics represents ethics in practice, i.e. transformation of general goals into concrete activities for the benefit of man. Ethics is an important principle in the service of mental health. According to the Declaration of Hawaii adopted by the World Psychiatric Association in 1977 and amended in Vienna in 1983, the goal of psychiatry is treatment of mental illnesses and promotion of mental health (Šegota 1994). A psychiatrist is obliged, to the greatest extent possible, to serve the needs of

his/her patients for their maximum benefit and stay in concordance with the accepted scientific knowledge and ethical principles as much as possible. At the same time they are obliged to pay attention to the general good and a fair distribution of health care resources. Ethics imposes the necessity of equal right to health for all. If it includes well-being according to the current WHO definition of health, then other various non-health related factors that contribute to well-being are also included. Keeping in mind numerous non-medical factors that affect human well-being, and primarily the inequality of allocation of resources: material, professional, human and even natural; it is understandable that the level of implementation of such a goal is subject to many, almost unsolvable, questions.

Comorbid states in psychiatry

Comorbidity in modern psychiatric practice is more a rule than an exception whether it were a psycho/psychic or psycho/physical comorbidity, irrespective of the cause-effect relationship. There are different combinations of comorbid states in psychiatry and they vary in frequency. Some of the more frequent psycho/psychic comorbidities are comorbid anxiety and depression, psychosis and depression, psychosis and addiction, PTSD and addiction and other (Pollack 2005, Chen et al. 2006). Mental illnesses and/or symptoms, among which the most frequent are depression, anxiety and insomnia, often occur alongside almost all more serious physical illnesses, such as cardiovascular illnesses, neoplasms, fibromyalgia, AIDS and other (Glassman et al. 2009, Arnold 2008, Colibazzi et al. 2006).

Psychopharmacotherapy, as well as other psychiatric and psychotherapeutic interventions in states and disturbances which do not primarily belong to the psychiatric range, are very specific for a number of reasons. Among other, we need to mention here the various chronic states of pain and the possibilities of a certain psychological control of pain which is moderated by the processes of psychological processing and involvement of an array of supraspinal mechanisms which participate in the change of perception of pain up to the final mental response (Gregurek 2006). There are also a number of iatrogenic reasons for the excessive comorbidity. Antipsychotic drugs and other medications that patients with schizophrenia must take, usually for many years if not for life, are associated with a number of side-effects such as weight gain, prolactin increase, cardiac effects, motor side-effects and blood dyscrasias, and, we must not forget, can have many untoward drug-drug interactions with other psychotropic and non-psychotropic drugs (Leucht et al. 2007). People with mental disorders were also reported to be less likely to be placed on HbA1c and cholesterol monitoring, to have a retinal examination to determine whether they have diabetes, to be treated for osteoporosis or to receive medical visits; and they are treated for a physical disease only if it is life threatening (Bishop et al. 2004). A problem with many current health systems is also that psychiatry is not integrated into a general medical setting, so that patients with psychiatric problems do not have adequate access to medical treatment. And in many psychiatric centres – especially in the developing world – there is a lack of resources for performing the appropriate laboratory examinations and treatment interventions (Leucht et al. 2007).

The high requests of medical science, the change of the relationships paradigm and the right to the welfare of the patient considerably define the relationships and the very process of making decisions about the application of psychopharmacs in this and similar situations. Together with the growth of evidence-based medicine there has been the publication of a growing number of guidelines and algorithms, including those in the area of psychiatry and psychopharmacology (Stein et al. 2005).

Since the states of chronic pain are at the same time states of stress for the patient, a special duty of the doctor and the supporting medical team is also consulting in the field of less known, but important fields of nutrigenetics and nutrigenomics, a field of science which takes a closer look at the mechanisms underlying diet-genome interactions and the potential application of nutritional genomics with the aim of improving the nutritional value of the food supply (Lucas-Schnarre 2008).

Pain is markedly disabling for an individual, it is frustrating, generates anxiety due to its uncertain possible intensity and duration, and it reduces the therapeutic relationship with the therapist to earlier levels.

On the other hand, the inability of the therapist to alleviate the pain can generate high emphatic capacities but also the trap of the doctor's hurt

narcissism because of a "personal" inefficiency. It is this very moment in the therapy alliance and the doctor-patient relationship that is very important for the correct interpretation of the efficiency of psychopharmacs in the treatment of pain and for avoidance of unnecessary "psychiatrization" of the doctor-patient relationship.

Pharmacotherapy of comorbidity requires the use of a greater number of different drugs that have complex drug-drug interactions and drug-patient interactions which can cause various side-effects in the patient. The factors related to the harmful side-effects of pharmacotherapy of comorbid states in psychiatry are the following: toxic effects of the drugs and/or additives contained in them; the patient's ability to metabolize and eliminate the drug; the patient's hypersensitivity; allergic reaction to a specific drug and/or additive; interactions of the drug with food or another drug; the context of drug administration; the patient's negative expectations and anxiety related to the treatment (e.g. extreme worrying, nocebo effect and pharmacophobia); the patient's willingness to cooperate; the establishment of a pharmacotherapy team between the psychiatrist and the patient; etc. An unavoidable factor of psychopharmacotherapy in general, especially of comorbid states (because of a greater risk of a wide array of side-effects caused by the combinations of drugs) is the ethical framework within which it is applied (Fitzgerald & Pharm 1999, Elkin 1999). Most psychoactive drugs circulate in the blood bound to various plasma proteins. For most drugs the percentage of total circulating concentration bound to proteins is quite high, frequently over 90%. It is a widely accepted principle that a free, non-protein-bound drug is the one which is available to distribute to target sites outside the circulation. The displacement of one drug from its protein-binding sites by another drug frequently results in only a transient change in free drug concentration which is buffered by a compensatory change in clearance or a change in bioavailability. Most psychoactive drugs are administered orally as it is expected that the concentration produced at the target sites of action will be high enough to be clinically effective. Numerous membranes, carrier proteins and enzymes interact with the orally administered drug. There are specific physiological mechanisms which either impede a drug's progress through the body or hasten its elimination (Stein et al. 2005).

The principal goal of modern pharmacotherapy of comorbid states is to find an optimal possibility of replacement of the so called dirty drugs, which cause significant side-effects and are little targeted to a specific pharmacotherapeutic activity, with the so called cosmetic, highly specific and potent psychopharmacs (Pakman 2003, Altman).

Psychiatric comorbidity in the evaluation of the overall state of health

Comorbidity in psychiatry, just like the mental illness itself, is a highly complex chronic state which requires a wider analysis and a multi-dimensional approach, often including numerous non-medical components. The doctor's approach to the patient, their relationship and the quality of the patient's life make a significant part of this process. One of the best descriptions of chronic states was given by Estroff: "Chronicity begins where a normal conversation ends, when a person has no one left who would listen to them" (Estroff 1989).

Today, psychiatric evaluation occupies an important place in the assessment of the overall state of health and quality of life, not only due to the fact that mental illnesses are almost always chronic or they gradually become such, but also because the prognosis of the physical illnesses that became chronic depends, in most cases, on the psychiatric comorbidity. Illness brings about a range of consequences: psychic, physical, even social limitations which over time become obvious to the degree that they surpass the boundaries of scientific interest of the reality-concept of chronic in medicine, gradually entering sociological and philosophical content (Stauber 2009). Psychopharmacological treatment of mental disorders has got to have its ethical component contained in the priority that the shift of attention is transposed from the micro-level of biological processes to the macro-level of human existence and well-being. Inadequate psychopharmacological treatment and/or bad compliance and adherence can lead to early development of chronic state of the illness, development of side-effects and comorbidity (Lage & Mariam 2009, Weiden & Rao 2005, Cramer & Rosenheck 1998).

From an ethical perspective, diagnosis and therapy preferences speak more about the time that passed, i.e. the time when they were made, than about the real and comprehensive psychosocial reality of the patient. In relation to that, static

attitudes should be replaced by curative ones in the context of time and the patient's needs (Stauber 2009).

Ethical and moral implications of psychopharmacotherapy

A moral philosophy of psychopharmacotherapy is in great extent connected to the safety, tolerance and acceptability of the drugs prescribed to a patient (Jakovljević 2009). It is in the context of biopsychosocial approach to the patient which is integrative (holistic) and individual, with a tendency of development into a biopsychospiritual concept (Aukst-Margetić & Margetić 2006). The basic moral questions that justify the applied psychopharmacotherapy are the patient's welfare and preference, optimal relationship between risk and gain for the patient, and some include cost benefit as well. Ethical questions related to psychopharmacotherapy emerge from the basic doctor-patient relationship, which is slowly changing from paternalistic concept which regards the patient as a passive object who merely listens and follows the doctor's directions, towards a partnership, a team relationship of cooperation between the doctor and the patient in which the patient takes an active part with a larger freedom of decision making, but also with the responsibility in the process of treatment (Talanga 2006, Ernst et al. 1996, Imber 2008).

A new clinical framework is formed based on informed consent and division of responsibility between the doctor and the patient in regard to the outcome of the treatment and prevention of serious side-effects of the psychopharmacotherapy. At this, the doctor is obliged to inform the patient about all the benefits and potential damages of the applied pharmacotherapy to his best knowledge and in the manner understandable to the patient.

Towards Hippocrates's psychopharmacotherapy

The context of fundamental Hippocrates's philosophy, i.e. the principle of Hippocrates's ethics, reflects the following clinical implications: 1. treating the illness and not the symptoms of the illness (later known as the Osler rule); 2. drugs are guilty until proven otherwise (later known as Holmes's rule) and 3. not all the diagnosis are created equally (later – the concept of diagnostic hierarchy) (Ghaemi 2008). Hippocrates's vs. non-Hippocrates's (Galenic) approach to psychopharmacology: Hippocrates's approach implies avoidance of drugs as much as possible, except when their role in curing the illness is clearly proven, giving at the same time great attention to their side-effects. On the other hand, Galenic approach implies primary use of drugs regardless of other aspects of treatment. The conclusion is that modern psychopharmacology is non-Hippocrates's, and there are some tendencies towards the return to Hippocrates's psychopharmacology. Accepting Hippocrates's approach does not signify being ethical, nor does belonging to non-Hippocrates's stream signify one is not ethical (Gilett 2004). Hippocrates's ethics stems from Hippocrates's philosophy of comprehension of illness and treatment; each doctor is free to accept such approach, and if they do not accept it they have a different view of illness and treatment, which is not, in itself, unethical. Thus, although not unethical, it is desirable to divert from the current classic orientation on primarily aggressive primary use of psychopharmacotherapy whose side-effects have a significant effect on the healing process and the patient's quality of life, especially in comorbid states, to an inclusion of a wider context of medical treatment and the patient's future way of life, in the context of holistic medicine which offers more answers.

Some bioethical questions of psychopharmacotherapy

There are some specific areas of psychopharmacotherapy ethics in some targeted populations such as children, adolescents and the elderly which have not been sufficiently explored yet (Koelch et al. 2008, Lakhan & Hagger Johnson 2007).

A noteworthy ethical question is the question of research in psychopharmacology. According to the current awareness the clinical research do not fit adequately into the framework of today's bioethics, are not completely benefitting the patients involved and divide the physicians into clinicians and scientists. Clinical research in psychopharmacology should by all means be supported, but within more defined ethical conditions (Ghaemi & Goodwin 2007).

Instead of conclusion...

Open questions for future discussion:

- Revision of the doctor-patient relationship as the foundation which generates all further ethical questions;

- Targeted search for cause-effect relationships of comorbid states;
- Ethical questions in psychopharmacotherapy of special targeted specific populations of patients such as children, adolescents and the elderly, which are rarely brought up;
- Ethics of clinical research in psychopharmacotherapy of comorbid states as a challenge to traditional bioethics.

REFERENCES

1. *Adizes I, The Pursuit of Prime. Santa Monica: Knowledge Exchange; 1996*
2. *Altman C. Ethical Implications of Cosmetic Psychopharmacology. http://altman.casimirinstitute.net/cosmetic.html*
3. *Arnold LM. Management of Fibromyalgia and Comorbid Psychiatric disorders. J Clin Psychiatry 2008; (2): 14-19.*
4. *Aukst-Margetić B, Margetić B. Religiosity and Health Outcomes: Review of Literature. Coll Antropol 2006; 29 (1): 365-371.*
5. *Bishop JR, Alexander B, Lund BC, Klepser TB. Osteoporisis screening and treatment in women with schizophrenia; a controlled study. Pharmacotherapy 2004; 24: 515-521.*
6. *Chen H, Reevs J, Fincham JE, Kennedy WK, Dorfman JH, Martin BC. Off-Label Use of Antidepressant, Anticonvulsant and Antipsychotic Medications Among Georgia Medicaid Enrollees in 2001. J Clin Psychiatry 2006; 67: 972-982.*
7. *Colibazzi T, Hsu TT, Gilmer WS. Human Immunodeficiency Virus and Depression in Primary Care: A Clinical Review. Prim Care Companion J Clin Psychiatry 2006; 8: 201-211.*
8. *Courtney H, 20/20 Foresight-Crafting strategy in an uncertain world. USA: McKinsey&Company; 2001*
9. *Cramer JA, Rosenheck R. Compliance With Medication Regimens for Mental and Physical Disorders. Psychiatr Serv 49: 196-201, February 1998*
10. *Džakula A, Vončina L, Laaser U. Capacity Strengthening for Administrative Decentralisation The European Union's CARDS Programme for Croatia, Zagreb, 2007*
11. *Elkin GD. Introduction to Clinical Psychiatry. Stamford, Conn: Appleton & Lange, 1999*
12. *Ernst E, Willoughby M, Weihmayr TH. Doctors' authority. British Journal of General Practice. 1996.*
13. *Estroff S.E. Self, Identity, and Subjective Experiences of Schizophrenia: In Search of the Subject. Schizophr Bull. 1989 15: 189-196*
14. *Fitzgerald WL, Pharm BS. Legal and Ethical Considerations in the Treatment of Psychosis. J Clin Psychiatry 1999; 60(19):59-65.*
15. *Ghaemi NS, Goodwin FK. The ethics of clinical innovation in psychopharmacology: Challenging traditional bioethics. Philosophy, Ethics, Humanities Med. 2007; 2(26): 1186.*
16. *Ghaemi NS. Toward a Hippocratic Psychopharmacology. Can J Psychiatry 2008; 53(3): 189-196.*
17. *Gilett G. Bioethics in the clinic: Hippocratic reflections. Baltimore (MD): Johns Hopkins University Press; 2004.*
18. *Glassman A, Bigger T, Gaffney M. Psychiatric Characteristics Associated With Long-term Mortality Among 361 Patients Having an Acute Coronary Syndrome and Major Depression. Arch Gen Psychiatry 2009; 66(9): 1022-1029.*
19. *Green & Kreuter. Health Promotion Planning. 3rd ed., Mayfield, 1999.*
20. *Gregurek R. Suradna i konzulitativna psihijatrija, psihijatrijski i psihološki problemi u somatskoj medicini. Zagreb: Školska knjiga; 2006*
21. *Imber JB. Trusting Doctors: the Decline of Moral Authority in American Medicine. Princeton: Princeton University Press; 2008.*
22. *Jakovljević M. The side effects of psychopharmacotherapy: conceptual, explanatory, ethical and moral issues - creative psychopharmacology instead of toxic psychiatry. Psychiatr Danub 2009; 21(1):86-90.*
23. *Koelch M, Schnoor K, Fegert JM. Ethical issues in psychopharmacology of children and adolescents. Current Opinion Psychiatry 2008; 21(6): 598-605.*
24. *Lage MJ, Mariam KH. The relationship between antipsychotic medication adherence and patient outcomes among individuals diagnosed with bipolar disorder: a retrospective study. Annals of General Psychiatry 2009; 8:7.*
25. *Lakhan SE, Hagger Johnson GE. The impact of prescribed psychotropics on youth. Clin Practice Epidemiology Mental Health 2007; 3(21): 1186.*
26. *Leucht S, Burkard T, Henderson JH, Maj M, Sartorius N. Physical Illness and Schizophrenia. Cambridge: Cambridge University Press; 2007*
27. *Lucas-Schnarre P. Nutrigenetics & nutrigenomics: market expert discusses the similarities and differences between these growing fields. Nutraceuticals World. May 1, 2008*
28. *Pakman M. A systemic frame for mental health practices. In: Prosky PS, Keith DV (Eds): Family Therapy as an Alternative to Medication- An Appraisal of Pharmland. Brunner Routledge, New York, 2003; 93-110.*
29. *Pollack M. Comorbid Anxiety and Depression. J Clin Psychiatry 2005; (8): 22-29.*
30. *Scott DC, Jaffe TD, Tobje RG. Organizational Vision,Values and Missionb. Menmo Park, CA: CRISP Publications, Inc.; 1993*

31. Šegota I. Nova medicinska etika (bioetika). Rijeka: Medicinski fakultet; 1994
32. Stauber JV. Treatment of chronic psychiatric disorders - Ethical and anthropological aspects. Nervenarzt 2009; 80:564-577.
33. Stauber JV. Treatment of chronic psychiatric disorders - Ethical and anthropological aspects. Nervenarzt 2009; 80: 566-575.
34. Stein D, Lerer B, Stahl S. (Ed.). Evidence-Based Psychopharmacology. Cambridge: Cambridge University Press; 2005.
35. Talanga J. Odnos liječnika i pacijenta prema medicinskoj etici. Zagreb: Bogoslovska smotra. 2006; 76(1): 47-59.
36. Weiden PJ, Rao N. Teaching Medication Compliance to Psychiatric Residents: Placing an Orphan Topic Into a Training Curriculum. Academic Psychiatry, 29:2, May-June 2005.

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