

NON-ADHERENCE TO MEDICATION: A CHALLENGE FOR PERSON-CENTRED PHARMACOTHERAPY TO RESOLVE THE PROBLEM

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SUMMARY

Pharmacotherapy today is claimed to be fascinating, scientific, rational, and objective, very much evidence-based, powerful and fundamental form of treatment for many medical conditions. Non-adherence to medication as an invisible epidemic is argued to be an Achilles' heel of evidence based medicine. Person-centered psychiatry has an important role in helping medicine to better understand human nature, human behavior and patients' choice in complex interactions. Non-adherence is a major target for interventions to improve the quality and outcomes of health care.

Key words: non-adherence with medication - person-centered medicine - person-centered pharmacotherapy

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INTRODUCTION

"Medications don't work in patients who don't take them"

Patient non-adherence to prescribed medication limits the effectiveness of treatment for many medical conditions. It is identified as an invisible epidemic, huge public health problem which has been an everlasting challenge throughout history of medicine. Hippocrates, around 400 BC observed that some patients did not take their medicines as prescribed, and later complained that the treatment was not effective. In the 19th century, Robert Koch, the father of modern bacteriology, criticized patients with tuberculosis who were non-adherent with prescribed treatment as "vicious consumptives, careless and/or irresponsible (see Hugtenburg et al. 2013). In 1955 it was reported that approximately one third of patients with acute pharyngitis and otitis media did not complete a one-week course of oral penicillin (see Haddad et al. 2014). Non-adherence to medication has been reported to range from 13% to 93%, with an average rate of 40% (see Nichols-English & Poirier 2000). Non-adherence rates vary with different diseases and different stages of disease; they are particularly high in patients with chronic diseases. So, it was reported that among patients with arterial hypertension non-adherence rate was 40%, whereas among patients with arthritis was even higher, between 55% and 70% (see Nichols-English & Poirier 2000). According to some research between 15% and 28.3% of patients do not fill a new prescription, of those who do fill a new prescription, approximately 50% discontinue medication in the first six months (see Solomon & Majumdar 2010, Gadkari & McHorney 2012). A meta-analysis of 569 studies confirmed that an average non-adherence rate was 25% (see Hugtenburg et al. 2013). In a sample of 24,017 adults with chronic disease who self-identified

as taking medications persistently, 70% reported at least one instance of unintentional non-adherence, and 34% reported at least one instance of intentional non-adherence in the past six months (Gadkari & McHorney 2012). A recent Canadian study showed that 31.3% of the 37,506 incident prescriptions written for the 15,691 patients in primary care were not filled (Tamblin et al. 2014).

Due to non-adherence or lack of persistence with medication substantial number of patients do not benefit optimally from their treatment, have worse health outcomes with increased morbidity and mortality what is all associated with increased societal costs. So, non-adherence to medication is argued to be an Achilles' heel of evidence based medicine (Gadkari & McHorney 2012). According to the World Health Organization (WHO) "increasing the effectiveness of adherence interventions may have far greater impact on the health of the population than any improvement in specific medical treatments" (Marcum et al. 2013). Non-adherence to medical treatment can be a severe problem that it is included in DSM-5 (APA 2013) as a diagnostic category V15.81 (Z81.18). Good news is that non-adherence to medication is a diagnosable, preventable and treatable medical condition from the perspective of person centered medicine and personalized pharmacotherapy.

DEFINITION AND CAUSES OF NON-ADHERENCE

"It is more important to know what kind of a patient has a disease than what kind of a disease a patient has"

(William Osler)

According to the WHO (2003) adherence to treatment is "the extent to which a patient's behavior: taking medication, following a diet, or making healthy

lifestyle changes, corresponds with agreed-upon recommendations from a health-care provider". In other words, adherence refers to an active, voluntary, and collaborative involvement of the patient in a mutually acceptable and respectable course of behavior to produce a therapeutic result (Ho et al. 2009). Medication adherence can be defined as the degree in which patients respect and follow recommendations about the daily timing, dosage, frequency and duration of medication use. Adherence similar terms used commonly as synonyms, although they have different and distinctive meanings, are compliance, concordance and persistence. Compliance refers to the extent to which the patient follows the recommendations of MD, but in one more passive way. That's why compliance today for many has the negative connotation of unequal power balance in which patients are subservient to MDs and passive objects of their treatment. Concordance refers to an agreement between the MD and the patient on the purpose and use of the medication, but this term is also used for appropriateness of medication intake behavior (see Hugtenburg et al. 2013). Persistence refers to the duration of taking medication if patients continue a treatment for the recommended period (Solomon & Majumdar 2010). So, persistence indicates how long patients stay in treatment, whereas adherence indicates how well patients implement the prescribed regimen (Hugtenburg et al. 2013). Adherence to medication can be complete when patients take each dose precisely on time or partial when patients take medications but miss doses from time to time. Adherence is usually defined for research purposes as taking at least 80% of the medication prescribed. Problems with adherence can involve the opposite phenomenon of taking excess medication.

Medication non-adherence has been usually met with the so-called "difficult" medication patients including the lack of insight patients, the minimal contact patients, the negative drug attitude patients, the patients preoccupied with side-effects and negative expectations from drug treatment, the suspicious and paranoid patients, the patients who need to be in charge, the misinformation overloaded patients, the nocebo responders, the defiant and stubborn patients, etc. (see Doran 2003, Haddad et al. 2014, Jakovljevic 2014a,b). There are several distinctive medication non-adherence phenotypes: 1. the patient does not understand the relevance of adherence with medication to continued health and well-being; 2. the patient has concluded the benefits of taking medications does not outweigh the costs; 3. the complexity of medication management exceeds the information processing capacity of the patient; 4. the patient is not sufficiently vigilant; 5. the patient holds inaccurate, irrational or conflicting normative beliefs about medications; 6. the patient does not perceive medication to have therapeutic efficacy (Marcum et al. 2013); 7. the patient is pharmacophobic; 8. the patients is demora-

lized; 9. the patient has masked or unrecognized depression. It seems useful to differ primary from secondary (see Solomon & Majumdar 2013), and intentional from non-intentional non-adherence (see Hugtenburg et al. 2013). When patients do not even fill a new prescription, it is defined as "primary" non-adherence whereas "secondary" non-adherence refers to cases when prescriptions are filled, but medication is not taken as prescribed. Lack of persistence refers to patients with good primary and secondary adherence who self-discontinue treatment by not refilling their prescriptions. Intentional non-adherence is defined as a process in which patients actively decide to be non-adherent with medications or with treatment recommendations. For example, with reading the patient information leaflet, patients may become skeptical or frightened about their medication because of negative side effects. Sometimes, using certain medication can be stigmatizing or reminding patients that they are ill. Intentional non-adherence to medication can be rational or irrational process in which the patient decides between pros and cons of the treatment. Unintentional non-adherence is passive action and refers to unplanned behavior which results in non-taking medication and not-following treatment recommendations, for example due to forgetfulness, carelessness or circumstances out of patients' control. Patients often exhibit both type of non-adherent behaviors (Gadkari & McHorney 2012).

According to the WHO (2003) many factors may be associated with poor adherence which may be classified in five distinct categories: 1. social and economic factors (eg, unstable living conditions, medication cost, lack of financial resources, burdensome work schedules, low health literacy); 2. healthcare system factors (eg, provider communication skills, provider-patient relationship, no care continuity); 3. medical condition-related factors (eg, chronic conditions, psychiatric disorders, lack of symptoms); 4. treatment-related factors (eg, complexity of medication use, medications with social stigma associated, duration of therapy, negative side effects); and 5. patient-related factors (patient negative beliefs about treatment, cognitive impairment, visual impairment). However, generally speaking fundamental cause of treatment non-adherence seems to be technical, impersonal, and only disease-, without person-, centered approach to treatment. Pharmacotherapy today is argued to be fascinating, scientific, rational, and objective, very much evidence-based, powerful and fundamental form of treatment for many medical conditions. However, rational and scientific pharmacotherapy is often equated with the therapeutic action of medicines in exclusively biological terms. Patients are commonly treated just as carrier of symptoms, diseased organs, failed body machines or biological objects that respond chemically to medications, but not also as subjects who respond to the meaning that those medications and medical conditions have for them. Due to impersonal treatment

model many patients complain on spirit breaking interactions with health professionals engendering feeling of being disrespected, discouraged and hopeless. Lack of positive therapeutic relationship, respect, trust and hope has detrimental consequences in terms of treatment non-adherence and prevalence of nocebo over placebo responses to treatment.

INTERVENTIONS TO IMPROVE ADHERENCE: PERSON-CENTERED MEDICINE AND PERSONALIZED PHARMACOTHERAPY

*„The good physician will treat the disease,
but the great physician will treat the patient“
(William Osler)*

Changing treatment philosophy is usually a critical step towards overcoming therapeutic stagnation, particularly that related to medication non-adherence. A “paradigm shift” is needed from the mechanistic, formistic and reductionistic way of thinking to creative, contextual and systemic thinking of person-centered medicine and personalized pharmacotherapy. Person-centered medicine has become a guiding principle in many countries which promotes a new culture of care and therapeutic relationships. Term person-centered medicine may have different meanings for different people. This concept of the person centered or personalized pharmacotherapy is based on medicine of person of Paul Tournier (see Cox et al. 2007), on creative pharmacology (see Bernstein 1995, Jakovljevic 2013a,b), on the art and practice of learning organization (see Senge 2006), and on positive psychology (Seligman 1998, 2012). Patients always bring into treatment unique personal characteristics, desires, needs, expectations, abilities, fears, etc. Disease has to be cured, but the person of the suffering patient has also to be met, helped and healed. So, in addition to disease demotion, treatment should be oriented toward wellness promotion. Person-centered medicine is related to working towards better health, regardless of the presence of medical conditions. It is closely associated with stress coping skills, self-care and self-management (Slade 2011). Self-care refers to the practice of activities that patients initiate and perform on their own behalf in maintaining life, health, and well-being; whereas self-management refers to activities which patients perform to live well with managing illness and utilizing resources. A normal life can be achieved through various self-management strategies focusing on life perspective („increase wellness, decrease illness” concept).

Person-centered pharmacotherapy includes always an individualized approach because each patient is a unique individual comprised of body, mind and spirit. Sensitivity to different medications varies from one individual to another. Genetics, personal history, particularly drug history and comorbidity may significantly

influence on individual response to medication treatment. The field of pharmacogenetics and epigenetics is a rapidly evolving science investigating the genotype as a possible reason for good, poor or no responding to drugs as well as for deleterious side-effects. When starting with pharmacotherapy, it is important to choose medications that 1. can treat comorbid conditions present, 2. have no a particular side-effect, 3. do not complicate a medical condition, 4. have no a negative interaction with another medications, 5. have side-effects that may be to the patient's benefit, 6. are preferred by the patient, 7. have been effective in a close relatives of the patient, 8. are affordable for the patient (Doran 2003). Each patient should get highly specific and individually adjusted drug treatment in given circumstances (Jakovljevic et al. 2010). Generally speaking, the optimal treatment regime, in terms of drug selection, dosage, duration, effectiveness (efficacy and tolerability) is individual and should be person-centred.

Pharmacotherapy is a context dependent practice because different contexts at many levels affect the meaning of biological variables in different ways. It is an important fact that “the genome operate within the context of the cell, the cell within the context of the body, the body within the context of the self, the self within the context of the society, the society within the context of the cosmos” (Cloninger 2004). The close interconnectedness of the spirit, mind, brain, endocrine and immune systems suggests a self-aware “operating” and “healing” system of human beings, which works silently in the background regulating and coordinating all living processes. Medications can produce changes at different levels, and vice versa their effects can be under influence within different contexts. Culture, community and different treatment contexts can affect treatment outcome. That’s why person-centred pharmacotherapy is firmly associated with creating favorable treatment context which promote therapeutic alliance and partnership. Person-centered pharmacotherapy is also a transculturally sensitive practice.

The psychology of prescribing and taking medications is very complex. Psychosocial aspects of pharmacotherapy may be as relevant as biological aspects in effecting positive treatment outcomes and full recovery. Assessing personality structure, attachment style, conflicts, needs, desires, dysfunctional beliefs, typical interpersonal patterns, conscious and implicit attitudes about medications, and the place of the sick role in the patient's life can help the prescriber to anticipate and deal problems and potential problems with medications (Mintz 2005). Such an assessment commonly makes patients feeling that the MD is interested in all aspects of the patient's life and not just the patient's symptoms. This alone may contribute to therapeutic alliance and and make it more likely that the patient will tell the MD her or his concerns before these concerns emerge behaviorally as medication non-adherence or other

problems (Mintz 2005). Patients are always subjects who give meanings and respond more or less actively to the meanings that disease, illness and treatment have for them and their physicians. Hence each treatment is associated with placebo (Latin word “I shall please) or nocebo (Latin word “I shall harm) response which can significantly modify the overall treatment outcome so these phenomena are of great importance for pharmacotherapy and medicine in general. Person-centred pharmacotherapy is placebo-response increasing and nocebo-response decreasing oriented practice. Person-centered medicine method for improving adherence can be remembered by the acronym SIMPLE: Select medications respecting the patient's preference and Simplify the regimen; Increase knowledge; Modify negative patient's attitudes and behavior; Provide person-centered pharmacotherapy and motivational interviewing; Leave paternalism and empower patients to self-manage their medical condition; and Evaluate adherence regularly.

CREATING FAVORABLE TREATMENT CONTEXT IS FUNDAMENTAL

“Homo homini remedium est”

In addition to the optimal treatment regime in terms of drug selection and dosage, creating specific favorable treatment context for each patients individually is an essential part of person centered pharmacotherapy. The term context refers to the particular setting, such as time, place and people present, that gives meaning to all events and activities during treatment. The fact is that in addition to physical world, we also live in the world of ideas, symbols and meanings. Certain actions are possible or positive in one context, whereas they are negative or not allowed in some other context. Nothing is either good or bad in itself and nothing has meaning only in itself, including mental health drugs application. Information or an event has always to be understood in the context so that the meaning we derive from any experience depends on the frame we apply. Many of the concepts of health, wellness and illness as well as the use of medications are often mysterious for patients and their families and filled with myths, misconceptions, prejudice and fears (see Jakovljevic 2013a). The patient's beliefs concerning the origin of symptoms and medicines action may contribute positively (placebo) or negatively (nocebo) to drug treatment response. In addition to their pharmacodynamic mechanisms, medications work also on account of meanings, expectations, and relationships. Hence, treatment effectiveness depends on 1. what MDs and patients believe how medications work, 2. quality of a physician-patient relationship including rapport (mutual trust and respect) and patient's confidence in the medicine as a whole, 3. characteristics of the treatment (color, shape, smell, taste and name of

medications, method and place of application, etc.); 4. communication and emotional expressiveness within the patient's family, 5. respecting patients' human rights. Always we should have in mind that “pharmakon”, which means both “remedy” and “poison” is closely related to “pharmakos”, which means “scapegoat” and to “pharmakeus”, “magician” or “sorcerer” (see Derrida 1982, Pakman 2003). Positive beliefs and good human relations may be “ariston pharmakon”, “most effective remedy”, whereas negative and wrong beliefs and bad human relations may be scapegoating. When beliefs are an expression of hubris, they can become more dangerous poison than any pharmakon. The creation of favorable treatment context as well as a creative collaboration with patient and her or his family may significantly improve treatment outcome increasing treatment adherence, enhancing placebo and decreasing nocebo response (see Jakovljevic 2014b).

The creation of favourable therapeutic context is significantly associated with active participation of patients and their commitment to treatment. The purpose of pharmacotherapy is to empower the patients to control their disease, to obtain full personal recovery and to regain control over their life. However, medications in general are often not enough for full treatment success.

Creation of the favorable treatment context is based on the human rights FREDA (fairness, respect, equality, dignity, autonomy) concept (Curtice & Exworthy 2010), shared decision model, shared vision of treatment goals and shared learning with patients (see Senge 2006). Learning in this context does not mean getting more information, but expanding the ability to produce the results truly wanted (Senge 2006) in drug treatment. Improving personal mastery, involving self-care and self-management of patients goes beyond competence and skills, as well as beyond spiritual unfolding or opening, it means living life from a creative as opposed to reactive viewpoint (Senge 2006). Creative collaboration with patients and their families includes building the shared treatment goals as well as the pictures of their future that foster their genuine commitment and enrollment more than simple compliance. Alliance is much more than compliance. A shared vision is the first step in allowing people who mistrusted each other to begin to work together (Senge 2006). Motivational interviewing with matching, pacing and leading techniques, is an essential step in establishing a creative treatment context because it helps the patients to articulate personally meaningful goals, while taking medications may facilitate achieving their goals. Being able to set and pursue personal goals provides much of the motivation for better cooperation and active participation in treatment. As patients develop more personal mastery over their symptoms, they become able to better master over their lives and to realize their own vision of recovery.

INCREASING PLACEBO AND DECREASING NOCEBO RESPONSE IMPROVES TREATMENT ADHERENCE

*Treat the disease, heal the illness
(Freeman 1993)*

Adherence with medication is associated with pharmacophilia and placebo response, whereas treatment non-adherence may be related to nocebo response to treatment. Causal factors of many psychosomatic disorders and diseases are linked to distressful life experiences and negative beliefs, views and expectations. As psychosomatic disorders may be provoked by negative expectations, pessimistic and fatalistic thinking they can be described in some way as a nocebo response to adverse life events. According to the model of learned helplessness and hopelessness repeated exposure to uncontrollable events with faulty learning due to negative attribution style leads to negative affectivity (low mood, loss of pleasure, feelings of guilt, irritability, anxiety), negative cognitions (negative view of the self, the world and the future, indecisiveness, self-devaluation, self-blame, hopelessness), negative motivations (loss of interest, suicidal drive, social withdrawal, and neglect of appearance and hygiene), behavioral changes (agitation, hypoactivity, psychomotor retardation) and vegetative changes (reduced libido, loss of appetite and weight, vague aches and pains). The concept of psychosomatic disorders as a nocebo reaction to life events may explain high rates of placebo reaction in psychosomatic patients. Psychosomatic disorders are a vicious circle in which pessimistic thinking, negative expectations and negative emotions feed on each other. Placebo response is related to positive expectations which can set in motion a positive cycle, in which positive fluctuations in mood and well-being are interpreted as evidence of treatment effect instilling a sense of hope.

PATIENTS SHOULD BE ACTIVE PARTICIPANTS IN THEIR PHARMACOTHERAPY

*Patients should be stars of treatment,
not a stage for medication trials*

There are many different reasons why patients take or refuse to take health medications. Besides the wish for resolving symptoms, patients may decide to take medications to please the spouse, to save their marriage, to keep their children satisfied, to save their job, to please clinician, because someone else (a friend, relative or celebrity) they respect has already tried medication and found it helpful, to prove that medications are not effective, to help in a lawsuit, claim for disability or child custody, to satisfy the courts or the law (Doran 2003).

The majority of patients who are resistant to treatment, relapsed or rehospitalized are intentionally or unintentionally non-adherent, completely or in some degree.

Active participation of patients in their treatment is an essential part of person-centered pharmacotherapy which may significantly contribute to better treatment adherence. Patients are not only carrier of symptoms, disease or illness, they are primarily human beings, persons and personalities with their power, autonomy, needs, values, desires purpose of life. Shared decisions and shared vision of therapeutic goals made in collaboration and alliance when patients assume that they are respected and valued as a person will facilitate patients' commitment to treatment goals and continued improvement. According to philosophy of person-centered pharmacotherapy patients should be stars of treatment, not a stage for medication trials and errors. Patients should be educated by their MDs regarding optimistic and realistic expectations for the effectiveness of medication therapy and achieving full recovery. Motivational interview, psychoeducation, informed consent and therapeutic contract should help patients to experience possible choice of treatment as his/her good choice. Motivational interview is a method used to explore barriers to medication adherence and to help patients decide to try prescribed medications and stay on them for recommended period. Motivational interview is not a method for tricking patients in doing what they do not want to do. It is a collaborative, evocative, and respecting patient autonomy clinical skill for eliciting from patients their own good will and for making behavior changes for the sake of their health (Rollnick et al. 2008). Motivational interview is person-centered method and has four guiding principle which can be remembered by the acronym RULE: Resist the righting reflex, Understand your patients' motivations, Listen to your patients, and Empower your patients. Successful motivational interview is based on a balance between directing, guiding and following the patient on the one hand and encouraging the patient to find optimal solutions on the other. It is well known psychological fact that there is something in human nature that resists being coerced and told what to do, whereas respecting people's right and freedom not to change sometimes makes change possible. Balance between core communication skills: asking, listening, informing, advising and supporting patients is of great importance. Helping patients decide to try medications and stay on them is an important goal of therapeutic contract.

Creation and fostering hope, meaning, personal responsibility, spirit of optimism and commitment can significantly contribute to overall positive response to pharmacotherapy, but in the other way round drug treatment can contribute to creation and fostering hope, meaning, personal responsibility, spirit of optimism and commitment. Hope, which includes perceived external resources, perceived internal resources and positive expectations, is recognized as the starting point for future treatment success. Patients with high hope are more likely to cope successfully with future adversity. Recognizing or finding meaning in life is fundamental issue for everybody, with or without medical condition, and it is associated with making sense of experience and generating a

story. The story is a natural framework for a very different conclusion about how we live and what we do; and what is the meaning of everything.

CONCLUSIONS

Patient non-adherence to prescribed medication limits the effectiveness of treatment for many medical conditions. Psychosocial aspects of pharmacotherapy seem to be as relevant as biological aspects in effecting positive treatment outcomes and full recovery. Generally speaking fundamental cause of treatment non-adherence seems to be technical, impersonal, and only disease-, without person-, centered approach to treatment. Good news is that non-adherence to medication is a diagnosable, preventable and treatable medical condition from the perspective of person centered medicine and personalized pharmacotherapy. A person-centered approach to pharmacotherapy recognizes that the healing process is more than chemical equilibration related to drugs bioavailability in the blood. Framing a positive therapeutic context in which medications are prescribed and used by patients is of a fundamental importance. Attention to promoting healthy life styles, general well-being, social integration and spirituality are very important elements of holistic and integrating treatment that enhances adherence to medication and favorable drug response.

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