

CREATIVE, PERSON-CENTERED AND NARRATIVE PSYCHOPHARMACOTHERAPY OR HOW TO PREVENT AND OVERCOME TREATMENT RESISTANCE IN PSYCHIATRY

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SUMMARY

Despite of the huge progress in clinical psychopharmacology and recent introduction of many new mental health medicines, a significant proportion of psychiatric patients do not respond satisfactory to pharmacological treatment. Such patients are commonly labeled "treatment resistant" although there is no full agreement about definition of the term. The precise prevalence of treatment resistance is hard to determine due to the lack of consensus regarding the term definition and too many cases of pseudo-resistance. Resistant and refractory mental disorders have significant economic, social, physical, and psychological consequences. The suffering and disability associated with chronic, unremitting mental disorders is profound. Changing treatment philosophy may be a critical step towards overcoming what some view as "therapeutic stagnation in psychiatry" and providing better treatment effectiveness and efficiency for patients benefit. A "paradigm shift" is needed from the mechanistic, formistic and reductionistic way of thinking of technical and impersonal psychopharmacology to contextual and systemic thinking with new treatment holodigm individualizing and personalizing psychopharmacotherapy in a more creative manner. Treatment resistance as a construct should be reconsidered as well as "monotherapy before polytherapy" treatment strategy. The best treatments are those that utilize and integrate multiple therapeutic modalities. The concept of creative, person-centered narrative psychopharmacotherapy gives a hope for increasing treatment effectiveness and efficiency in psychiatry.

Key words: treatment resistance - difficult-to-treat mental disorders - treatment response – personal recovery - narrative psychopharmacology - creative person-centered psychopharmacotherapy

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INTRODUCTION

"Positive psychiatry – a psychiatry that aims not just to reduce psychiatric symptoms but to help patients grow and flourish – is the future"

Dilip Jeste, in his address at the APA's annual meeting on May 6, 2012

Treatment resistance is one of the very challenging issues in contemporary psychiatry. It represents a source of significant clinical and nosological controversy and confusion. Treatment insufficient response and treatment failure occur across the wide spectrum of mental disorders causing huge emotional sufferings and enormous economic and social costs. In spite of the great progress in clinical psychopharmacology and evidence that mental health medications may significantly alleviate the huge suffering and burden caused by mental disorders, therapeutic outcome for many psychiatric patients has remained poor. Numerous studies clearly demonstrate that a great proportion of psychiatric patients achieve only partial improvement or no improvement in their symptoms, many of them suffer adverse and even toxic effects of drugs. Given the lack of consistence in defining criteria, it is difficult to assess the accurate prevalence of treatment resistant mental disorders. Depending on the definition between 30% and 60% of patients with schizophrenia are considered treatment resistant (Riva Posse & Nemeroff 2012). Refractoriness to standardized treatment can be seen in about a quarter patients with schizophrenia who adhere to standard

treatment protocols (see Sarkar et al. 2014). Less than half of depressed patients starting a course of anti-depressant treatment will reach remission with that treatment (Parikh & Lebowitz 2004). Approximately one out of three patients with diagnosis of anxiety disorder is resistant to standard psychopharmacotherapy. One can assume that 30% of patients would be considered recovered from the standard treatments, 30-40% of patients would be considered improved, whereas 30% of the patients would be barely touched by the contemporary treatments (Bystritsky 2006). The probability of remission of generalized anxiety disorder is only 15% after 1 year and 25% after 2 years (Riva Posse & Nemeroff 2012). Between 40 and 60 percent of patients with obsessive-compulsive disorder (OCD) do not respond in satisfactory way and an even greater proportion of OCD patients fail to reach complete remission after a first trial (see Albert et al. 2013). Patients with residual symptoms have poorer long-term outcomes and increased relapse risk. According to some opinions, inadequate treatment is often the rule rather than the exception in the treatment of mental illness (Riva Posse & Nemeroff 2012). Relationship between illness chronicity, treatment non-response and treatment resistance/refractoriness is circular and complex one. Illness chronicification is commonly associated with insufficient treatment response. Major mental disorders are typically chronic disorders with a waxing and waning course. Psychiatric patients who do not achieve a full symptomatic remission have higher probability of relapse or new episode of illness.

Table 1. Terminology and operational definitions related to the lack of satisfactory treatment response

Treatment nonresponse: A response that is not significant or is poor enough such that a change in treatment plan is required.

Lack of response: Failure to reduce of at least 50% in the symptom severity.

Treatment response: A response that is good enough such that a change in treatment plan is not required.

Insignificant response: 25-49% symptom reduction from baseline.

Response without remission: 50% or greater symptom reduction from baseline but without achieving full remission.

Full therapeutic response: Attainment of asymptomatic stage.

Insufficient therapeutic response: Non-attainment of asymptomatic stage.

Remission: Attainment of asymptomatic stage or enough significant improvement.

Partial remission: 50-75% symptom reduction.

Full remission: Attainment of asymptomatic stage for 2 consecutive months.

Recovery: Remission for at least 6 consecutive months.

Clinical recovery: Attainment of asymptomatic stage for at least 6 consecutive months; measured by symptom remission, insight gain, absence of relapse, ability to carry out daily living activities and a return to work or study.

Incomplete recovery: The term preferred by some experts to the term treatment resistance.

Personal (mental health) recovery: A journey of healing and transformation enabling a person with a mental disorder to live a meaningful life in the community of his or her choice while striving to achieve his or her full potential of self-actualization. It is a way of living satisfying, hopeful, and contributing life even with the limitations caused by illness.

Relapse (refers to the same episode): Return of symptoms within 6 months of remission.

Recurrence (refers to the new episode): Return of symptoms during recovery period.

Pathology breakthrough: Return of symptoms during continued mental health medication.

Treatment-resistance: There has been only a partial response to treatment; patient meets criteria for response, but not for remission.

Treatment-refractoriness: There has been no response to treatment; symptoms unchanged or worse.

Absolute treatment resistance: Nonresponse to an adequate treatment.

Relative treatment resistance: Nonresponse to an inadequate treatment.

Treatment pseudoresistance: Nonresponse to inadequate drug treatment, in terms of duration or dose of the mental health medicine used.

Difficult-to-treat mental disorders: A failure to respond to one or more adequate trials of mental health medications. This term covers treatment resistant and treatment refractory mental disorders and severe mental disorders.

Incurable mental disorders: Mental disorders without remission in spite of adequate treatments.

Treatment efficacy: 1. The ability of treatment to produce the desired therapeutic effect; 2. The extent to which a treatment intervention produces a desired amount of the desired effect under controlled circumstances.

Treatment effectiveness: 1. The extent to which a treatment intervention produces the desired therapeutic effect without adverse events and undesirable side-effects; 2. The ability of a treatment intervention to produce the desired beneficial effect under ordinary circumstances.

Treatment efficiency: The ability of a treatment intervention to produce the desired beneficial effect in the most economical way with little wasted resources (good input to output ratio).

Treatment tolerance: The ability of treatment to produce the therapeutic effects without concomitant adverse events and undesirable side-effects (good risk-benefit ratio).

Treatment intolerance: Treatment compromised by dangerous side-effects (poor risk-benefit ratio).

Due to the high rate of treatment failures, the effectiveness of mental health medicines and rigid pharmacocentric treatment are currently in contention, both outside and within the field of psychiatry. Some classes of mental health medicines, for example antidepressants, are depicted as placebos with adverse effects, contributing so to vilification of contemporary technical and impersonal psychopharmacotherapy and stigmatization of psychiatry. There has been an increasing concern that clinical psychopharmacology has lost its right way. The time is ripe for psychiatry to find its transdisciplinary integrative soul and increase treatment effectiveness. Creative, person-centered and narrative psychopharmacotherapy gives a hope providing the tools needed to take science in perspective and keep person, understanding, ethics and personal recovery at the forefront of clinical practice.

DEFINITIONS AND CAUSES OF INSUFFICIENT TREATMENT RESPONSE IN CLINICAL PSYCHOPHARMACOLOGY

“What is effective is not always efficacious, and what is efficacious is not always efficient.”

Postulate on effectiveness

There is a growing body of knowledge on treatment-resistant major psychiatric disorders, but little consensus on how to operationally define the concept or on the optimal instrument to measure it (see Nemeroff 2012). Some scholars have proposed that treatment resistance and treatment refractoriness represent two separate states which should be given different criteria (Table 1). Both of these two words have very different meanings in psychiatry, full of controversies and confusion. Treatment resistance, for example, may refer to 1. non-adherent

Table 2. Some definitions of treatment resistance for different mental disorders

Recovery in schizophrenia is defined as a 2-year duration of 1. remission of symptoms; 2. engagement in productive activity such as work or school; 3. independent management of day-to-day needs; 4. cordial family relations; 5. recreational activities, and 6. satisfying peer relationships (Lieberman 2008)

Treatment-resistant schizophrenia was defined by the following two criteria: 1. at least three periods of treatment in the preceding 5 years with antipsychotics from at least two different chemical classes at dosages equivalent to or greater than 1000mg/day of chlorpromazine for a period of 6 weeks, each without significant symptomatic relief, and 2. no period of good functioning within the preceding 5 years (Kane et al. 1988).

Treatment-intolerant schizophrenia: If patients do not tolerate chlorpromazine-equivalent dose of 600 mg/day (Suzuki et al. 2012).

Treatment-resistant schizophrenia was defined by the following criteria: 1. clearly documented, unequivocal history of treatment failure with at least 2 different antipsychotics; 2. clearly documented history of treatment failure with at least 1 antipsychotic, together with prospective validation of treatment failure with at least 1 antipsychotic of physicians choice (other than the previously failed antipsychotic). Requirement in dose and duration: Each treatment with an AP has continued at CPZ-equivalent doses of at least 600mg/day for at least 6 consecutive weeks; Requirement in Rating Scales: Each treatment has resulted in a failure defined with both CGI-severity of at least 4 and more PLUS a score of at least 49 and more on FACT-Sz or at least or more on GAF (Suzuki et al. 2012).

Treatment refractoriness in schizophrenia according IPAP (2008): 1. no period of good functioning in previous 5 years; 2. prior non-response to at least two antipsychotic drugs of two different chemical classes for at least 4-6 weeks each at doses at least or more of 400mg equivalents of chlorpromazine or 5mg/day risperidone; 3. moderate or severe psychopathology, especially positive symptoms, such as conceptual disorganization, suspiciousness, delusions, or hallucinatory behavior (see Ballon & Lieberman 2012).

Treatment-resistant depression: Treatment non-response (ie, persistence of significant depressive symptoms, or less than 50% reduction in HAM-D score) despite at least two treatment trials with drugs from different pharmacological classes, each used in an adequate dose for an adequate time period of at least 4 consecutive weeks of treatment during which the patient has had an adequate dose for at least 3 weeks (Al Harbi 2012). Remission: reduction in HAM-D score for 75% and more; response: reduction in HAM-D score for 50% and more, but less than 75%; partial response: reduction in HAM-D at least 25%, but less than 50%; no response: reduction in HAM-D score less than 25%.

Treatment-resistant depression refers to major depressive episodes that do not respond satisfactorily to at least two trials of antidepressant monotherapy whereas the term treatment refractory depression typically refers to unipolar major depressive episodes that do not respond satisfactorily to numerous sequential treatment regimens.

Treatment-resistant bipolar disorder is generally defined as lack of optimal mood stabilization in acute episode of mania or depression or lack of recurrent mood episode prevention (Frye 2012). Bipolar I depression resistance is defined as nonremission despite adequate dose and duration of lithium treatment, lamotrigine augmentation of ongoing mood stabilization, or full dose, 600mg or greater, quetiapine monotherapy. Refractoriness is defined as further failure to reach remission with olanzapine/fluoxetine or lamotrigine/quetiapine combination treatments. Intractability is defined as further failure to achieve remission with adjunctive antidepressant, modafinil or pramipexole combinations therapies. Bipolar II depression has similar gradation of treatment failure, but it includes MAO inhibitor antidepressant in the definition of intractability (Pacchiarotti et al. 2009).

Treatment-resistant obsessive-compulsive disorder: full response is defined as 35% or greater reduction of Y-BOCS or CGI I or 2; partial response as greater than 25% but less 35% Y-BOCS reduction; non-response as less than 25% Y-BOCS reduction and CGI 4. Recovery is defined as a complete and objective disappearance of symptoms, corresponding to Y-BOCS value of 8 or below; remission can indicate a response that reduces symptoms to a minimal level, i.e. Y-BOCS score of 16 or less, being this value the minimum threshold one for a patient to be included in a clinical trial (Albert et al. 2013).

Social anxiety disorder can be considered as refractory or treatment resistant “when there are residual symptoms or when symptoms do not improve at all after some form of therapeutic intervention” (Pollack et al. 2008): a cutoff score of 30 (Ballenger 2001) or 36 (Bandelow et al. 2006) on the Liebowitz Social Anxiety Scale (see Bui & Bollack 2012).

Treatment resistance in PTSD can be defined as a failure to respond optimally to first line treatments (Louw & Stein 2012)

AP: antipsychotic; CGI: Clinical Global Impression; FACT-Sz: Functional Assessment for Comprehensive Treatment of Schizophrenia; GAF: Global Assessment of Functioning; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale; IPAP: International Psychopharmacology Algorithm Project

patients who are consciously or unconsciously resisting the treatment because of fear or unwilling to change themselves (psychological resistance); 2. patients who are motivated to change themselves and receiving adequate drug treatment but failing to achieve remission (true resistance); 3. patients who are motivated to change themselves but receiving non-adequate treatment and consequently failing to achieve remission (pseudo-resistance). Definition of treatment resistance is reversely related to the defining of treatment goals, remission, and recovery. Problems of defining treatment response, treatment adequacy, remission, minimal duration of remission and treatment resistance are clearly different considering clinical compared to research context. The research objectives refer to validation of

the concept with operational criteria for identification of predictive factors during biological studies or drug trials. In the clinical context, defining therapy resistance is mainly focused on recognition, diagnosis and treatment alternatives. Unfortunately, for the time being there is very little conceptual and terminological consensus about this important debated issue. A standard definition of treatment resistance in general as well as for specific mental disorders is still missing what causes many problems in clinical research and everyday practice. In the literature treatment resistance is broadly defined as a failure to respond completely or satisfactory to a standardized treatment, or as a failure to respond to at least two adequate drug trials. In clinical practice, treatment resistance can be presented along a

continuum ranging from partial response to complete refractoriness. The degree of treatment resistance is estimated by taking into account total number of medication trials and their outcome, the number of failed treatments, and the degree of lack of response. Similar, related to and associated with the treatment resistance and treatment resistant mental disorders are terms like difficult-to-treat mental disorders and difficult patients (Koekkoek et al. 2006). Terminology and operational definitions for the lack of satisfactory treatment response or insufficient treatment response are shown on tables 1 and 2.

Treatment resistance is a pessimistic term which may have double meaning: that the patient is resisting treatment and that the mental disorder is resistant to treatment. Treatment resistance implies negative and pessimistic message that nothing can be done to get remission or recovery. However, in clinical practice with regards to achieving desired treatment outcome after previous several unsuccessful attempts, transient treatment resistance in fact means “more difficult than usual treatment”. Therefore, treatment resistance is better viewed as treatment failure, unsatisfactory or incomplete treatment response offering a hope for better treatment success in the future. Learned helplessness and pessimism are essential features of some mental disorders, like depression and anxiety disorders. Optimism is regarded as an indication of mental health associated with higher level of subjective well-being. Furthermore, optimism may serve the function to motivate patients in the service of their active and cooperative participation and partnership in the treatment. Positive expectations and optimism are associated with placebo response as well as negative expectations and pessimism are related to nocebo response (Jakovljevic 2014a,b). It is essential for clinicians to balance the need to instill hope and optimism with realistic expectation for treatment response and outcome. Being therapeutically overzealous and offering unrealistic expectations may be very counterproductive.

Differentiation between true treatment resistance and pseudoresistance is of great importance (Atiq 2006). At clinical context, treatment adequacy in terms of medication choice, dose, duration and adherence to treatment is a substantial issue in dealing with treatment nonresponse. More than half patients referred for an evaluation of insufficient or lack of therapeutic response is assumed to have had inadequate trials of mental health medication. Rigid insisting on drug monotherapy rooted in simplistic thinking and failure to provide appropriate treatment, for example, prescribing inadequate doses of medicines, treating for too short time, are major causes of pseudoresistance. Factors on patients' side that frequently contribute to pseudoresistance involve premature discontinuation of medications due to adverse effects or treatment nonadherence due to pharmako-phobia or negative attitudes toward medication. Blood levels of mental health drugs should be determined if available in unresponsive patients to evaluate possible individual differences in pharmacokinetics and patient adherence to treatment.

Table 3. Treatment-resistance staging

Stage 1	Failure of an adequate trial of a 1 class of mental health medicine; duration of trial: 12-16 weeks.
Stage 2	Failure of adequate trial of 2 distinctly different classes of mental health medicine; duration of trial: 18-24 weeks.
Stage 3	Stage 2 plus failure of a third class of mental medicine; duration of trial: 24-32 weeks.
Stage 4	Stage 3 plus failure of an adequate trial of a fourth class of mental health medicine; duration of trial: 30-40 weeks.
Stage 5	Stage 4 plus failure of an adequate course of electroconvulsive therapy; duration of trial: 36-52 weeks.

Chronic resistant mental disorder:

Resistance to several medication trials, including augmentation, supplementation and combination strategies

Thase & Rush 1997; Connolly & Thase 2012; (modified and generalized)

Table 4. Approaches in the management of insufficient treatment response

Pharmacological strategies:

- *Increasing the dosage of medication* to the maximal recommended dose;
- *Switching strategies:* stopping the medication to which the patient is not responding and prescribing another medicine, usually from an another group of the same class;
- *Augmentation strategies:* adding another agent to an ongoing medication that has been insufficient;
- *Supplementations* (vitamins, omega-3fatty acids, amino-acids, S-adenosyl-L-methionine (S-AMe), Saint John's wort, ginko biloba, etc.);
- *Combination strategies:* using two or more compounds with a well-established efficacy as a single agent for the treatment of the mental disorder.

Non-pharmacological strategies:

- *Electroconvulsive therapy (ECT)* – better term *electroneuromodulatory therapy*;
- *Vagus nerve stimulation*;
- *Transcranial magnetic stimulation (rTMS)*;
- *Psychotherapy and psychosocial treatments*;
- *Psychological strategies:* respecting the patient, being nonjudgmental, careful active listening, validating feelings and behaviors, supportive and understanding attitude, framing a clear treatment strategy and contract; enhancing motivation for change (motivational enhancement therapy).

Integrated strategies:

- *Use of mental health medications together with other modes of treatment* like psychotherapy, family therapy, narrative therapy, risk management strategies, complementary and alternative medicine;
- *Creative, person-centered narrative psychopharmacotherapy*

Treatment resistance is not a static but evolving phenomenon. Some authors have proposed treatment-resistance staging model based on the idea that treatment resistance can be conceptualized along a continuum with regards to the number of previous trials and hierarchy of medications. The minimum criteria for treatment resistance used commonly in clinical trials is a history of nonresponse to at least two adequate drug

Table 5. Comparison of traditional and creative person-centered narrative psychopharmacotherapy with regards to treatment resistance and treatment non-response

<i>Traditional psychopharmacotherapy</i>	<i>Creative person-centered narrative psychopharmacotherapy</i>
<ul style="list-style-type: none"> ▪ Standardized, impersonal and dismissive of individuality ▪ Epidemiological and more scientific (modern science) ▪ Based more on linear, formistic and mechanistic thinking and deductive logic ▪ Self-determination of patients is limited; patients are more objects of treatment; compliance is expected or requested ▪ Only psychiatrists have access to information (e.g., drug treatment plans, assessments, records, etc.); “doctors know the best” ▪ Focus is on pathology (disease or illness), weakness and disadvantages; decrease illness ▪ Symptoms, dysfunctions, disabilities, deficits drive treatment; clinical (symptomatic and functional) remission is valued; drug treatments are primarily defined by treatment guidelines ▪ Avoidance of risk (“Primum non nocere”). Protection of patients and community ▪ Evidence-based practice ▪ “Monotherapy before polytherapy” strategy ▪ More pessimistic concepts; terms like treatment resistance, treatment refractoriness, incurability of major mental disorders ▪ Treatment goals: clinical remission, social recovery, relapse prevention ▪ Psychopharmacotherapy separated from psychotherapy 	<ul style="list-style-type: none"> ▪ Pluralistic, personal and respective of individuality and personal life stories ▪ Individualistic and more humanistic (postmodern science) ▪ Based on systemic, creative and lateral thinking, imagination and inductive logic ▪ Self-determination of patients is promoted; patients are more subjects, active participants and stars of treatment; alliance is much more than compliance ▪ Patients and their families have also access to the information. Doctors and patients together know what is the best, shared decisions; patients are best experts on their life ▪ Focus on self-actualization, health and quality of life, strengths and advantages; increase wellness ▪ Therapeutic goals drive treatment. In addition to clinical remission, personal recovery is valued; drug treatment is rooted in creative and systematic thinking in addition to treatment guidelines ▪ Responsible benefit-risk ratio evaluation; personal growth ▪ Both “evidence based-practice and practice-based evidence; value- and narrative-based practice ▪ “Polytherapy as soon as needed” strategy ▪ More optimistic concepts; terms like insufficient or incomplete treatment response, lack of treatment response ▪ Treatment goals: clinical remission, social recovery, personal recovery ▪ Psychopharmacotherapy closely joined with psychotherapy

trials during the current episode of the mental disorder. A practical system for treatment-resistance staging based on previous courses of treatment which can be used as a guide for applying prevention and treatment strategies is shown on table 3 (Connolly & Thase 2012). It should be noted that the evidence to guide clinical practice for specific mental disorders is limited. Therefore, it is important for clinicians to be optimistic and creative as well as to provide balanced hope (Connolly & Thase 2012). Furthermore, it is also important for clinicians to have in mind specific mental illness staging with regards to evaluation of treatment response or treatment failure. Old strategy “wait and see” has been replaced with “as early as possible” drug treatment in order to prevent mental disorders to become chronic illnesses.

According to current treatment guidelines there is quite a number of empirically supported strategies to relieve treatment non-response or failure and prevent developing treatment resistance (Table 4). First and foremost, clinicians should be rethinking their treatment strategy. The best treatments are those that utilize and integrate multiple modalities. The concept of creative, person-centered narrative psychopharmacotherapy gives a hope for overcoming treatment nonresponse and failure.

CREATIVE PSYCHOPHARMACOTHERAPY INCREASES TREATMENT EFFECTIVENESS AND DECREASE PROBABILITY OF TREATMENT NONRESPONSE

The ways in which we define problems in a clinical context often hinder their solutions

Paul Watzlawick 1989

There are three closely related terms very important in clinical psychopharmacology: treatment efficacy, treatment effectiveness and treatment efficiency (see table 1). Treatment effectiveness has been regarded as a degree of achievement in four domains: decreasing or eliminating symptoms of mental disorder (measured by using symptoms scales), treatment burden (measured by adverse event scales), disease burden (assessed by patients and their families) and wellness and health (measuring by quality of life scales). It’s one thing to wish or know what to do, another to be able of doing it and third to do it. Most important is the third – to do it, what here means to achieve desired treatment goals.

Treatment success is measured by treatment results, not by our theories, plans, intentions, promises or strict keeping treatment guidelines. Creative psychopharmacotherapy is a theoretical concept of the therapeutic journey

Table 6. Factors contributing to insufficient therapeutic response and treatment failure

1. *Illness-related factors:* poor knowing of pathophysiology, unrecognized and undiagnosed psychopathology, unrecognized comorbid medical disorders; comorbid psychiatric disorders (dual diagnosis); character pathology, deficiencies in thiamine, vitamin B6, vitamin B12, folate, copper, zinc.
2. *Treatment-related factors:* Non-adequate treatment, uni-modal treatment not covering some important pathological mechanisms, rigid dogmatic treatment approach.
3. *Medication-related factors:* delayed treatment onset, intolerance to the medication, adverse events and toxic side effects, monotherapy non-covering all important pathological mechanisms, irrational polypharmacy.
4. *Patient-generated factors:* partial adherence or non-adherence to treatment, rapid or slow drug metabolism; pessimism and negative beliefs and expectations, lack of faith in doctor and treatment, nocebo response, negative meaning response, negative treatment conditioning, negative therapeutic reaction related to unconscious sense of guilt, self-defeating behavior, pharmacophobia, prejudice, bad nutritional status.
5. *Clinician-related factors:* poor fit between type of psychological approach and personality type of patient; nocebo induction; lack of optimism; non-adequate communication style; lack of empathy, compassion and guidance skills; low level of experience and professional knowledge; discomfort with uncertainty; negative countertransference (anger, guilt, dislike, disappointment, helplessness, and powerlessness) and negative emotional reaction to the patient; unsatisfactory self-management; accusing the patient of being problematic or difficult.
6. *Factors associated with doctor-patient relationship:* anti-therapeutic relationship, lack of therapeutic alliance, psychiatric care experienced as impersonal, unconcerned and uncaring, lack of rapport, power games.
7. *Patient's family related factors:* stigma, lack of support and care, rejection, high negative emotional expression, family psychopathology.

through three phases: acute phase, stabilization phase (continuation treatment), and relapse prevention phase (maintenance treatment) searching for very high “therapeutic to side effect ratio” in efficient way in order to reach wanted destination of personal recovery as soon as possible. After acute phase of treatment there are five possible outcomes: 1. full therapeutic response without adverse events; 2. full therapeutic response with more or less adverse events; 3. partial therapeutic response without adverse events; 4. partial therapeutic response with more or less adverse events; and 5. no therapeutic response. The goal of creative psychopharmacotherapy is to maximize benefits and minimize undesired effects and adverse events.

Concept of creative psychopharmacotherapy provides an overarching theoretical framework that permits the integration of different levels of explanation from neuroscience, clinical psychopharmacology, psychodynamics, evolutionary psychobiology and positive psychology with practical implications in everyday clinical practice. It represents an art and practice of the learning organization in the frame of transdisciplinary, integrative, narrative, the person-centered and neuroscience based psychiatry (Jakovljevic 2010, 2013a,b 2015). It is relational,

Table 7. General principles for the management of treatment resistance

- Assess factors contributing to treatment resistance
- Ensure accurate diagnosis, including the subtype of mental disorder
- Assess psychiatric and somatic comorbidity
- Evaluate psychosocial stressors and enhance social support
- Ensure appropriate dose and duration of treatment (e.g. long-acting injectable antipsychotics)
- Assess drug induced neurotransmitter dysbalance syndrome, neurotransmitter receptor
- Supersensitivity syndrome (e.g. dopamine supersensitivity psychosis)
- Monitor and treat adverse events
- Ensure the psychoeducation of patient and his or her family
- Ensure treatment adherence and alliance
- Ensure integrative and complementary treatment approach
- Aim for personal remission/recovery

contextual, multimodal, personalized and individualized application of the creative thinking and systemic information processing strategy (see table 5). Creative psychopharmacotherapy includes not only creative and rational use of mental health medicines and their combinations, but also creating favorable treatment context, re-constructing narratives that fuel mental health problems and fostering patients’ creativity and personal mastery. It is an alternative to dogmatic, rigid and authoritarian application of official treatment guidelines and marketing based practice. National and international consensus treatment guidelines are needed and necessary, but still of limited benefit because they offer very little to guide clinicians as to make choices between available drug treatments.

Creative psychopharmacotherapy is much more than prescribing mental health medicines in rational manner and careful control of their use. It is transdisciplinary, multidimensional and multimodal, integrative therapeutic approach aimed to increasing treatment effectiveness and efficiency in everyday clinical practice. Treatment related effects may be specific and non-specific and classified in four categories: 1. drug-generated effects (pharmacodynamic effects); 2. patient-generated effects; 3. clinician generated effects; 4. the effects generated by the doctor-patient relationship. The more positive specific and non-specific therapeutic effects are induced, the better treatment outcome will be produced. There are also many diverse factors that may contribute to insufficient therapeutic response and treatment failure (see table 6). Creative psychopharmacotherapist addresses and manages these factors in order to avoid or overcome possible treatment failure (see table 7) and achieve full personal recovery.

Although many evidence support “polytherapy as soon as needed” strategy, international consensus treatment guidelines for all major mental disorders strongly recommend monotherapy as the first-line treatment in

spite of the fact that many psychiatric patients do not recover after their initial monotherapy trial. Approximately half of depressed patients, for example, show an insufficient response to monotherapy and every fifth patient has chronic depression despite of multiple interventions. General strategy “monotherapy before polytherapy” is one of the significant causes of treatment resistance, or better to say pseudo-resistance. It is evident that finding the right medication for an individual in serial monotherapy approach is not so easy. Many patients usually try several different medicines before finding the right one. In addition, we are now confronted with the fact that mental disorders are the result of abnormalities in the complex interactions between several neurotransmitter and psychobiological systems rather than in the abnormalities of any only one simple system. In clinical practice it is very difficult to achieve a full remission or recovery with drug monotherapy, so polypharmacy of mental health medicines should be rather a rule than an exception. Good clinicians practice rational polypharmacy, and those who do it expertly are leaders in their field (Doran 2003). It is quite rational to treat depressed patients with two or more antidepressants simultaneously if they have different mechanisms of action and synergistic therapeutic effects, e.g. stimulating one in the morning, and sedating one in the evening. It is similar with combinations of mood stabilizers, antipsychotics, etc. Many bipolar patients simply cannot be stabilized with one mood stabilizer alone, but improve considerably or achieve a full recovery when treated with a combination of mood stabilizers from different drug families. A common example of monotherapy ineffectiveness may be seen in bipolar depressed patients, when patients on a mood stabilizer alone have breakthrough depressions, but when on an antidepressant alone have lack of response, manic overstimulation or erratic, unpredictable response (Doran 2003). Rational combination of two or more mental health medicines may help patients to be mood stable and free from depression. Comorbidity is also an important reason supporting the rationale of polypharmacy. For example, patients with comorbid depression and anxiety disorder, like panic disorder, treated with antidepressant alone may become overstimulated or respond only partially, while treated with a high potent benzodiazepine alone may have breakthrough depressive symptoms or breakthrough panic attacks (see Doran 2003). Combination of these two classes of drugs together (COMBOs) may eliminate both depression and panic attacks. In general, creative COMBOs with an additive, synergistic therapeutic effect between two or more medicines make the overall treatment benefit greater than that achieved by either of the medications alone. For example, patients with panic disorder respond better and sooner to an antidepressant and a high potent benzodiazepine COMBO than to either of the medicines alone. When panic attacks disappear soon, the benzodiazepine is excluded, while maintenance treatment is continued with the antidepressant. As mental disorders

contribute enormously to psychological, social and economic suffering of patients and their families, the achieving as soon as possible complete remission is very important goal of creative psychopharmacotherapy. Rapid remission and complete recovery can be achieved in majority cases only with rational drug combinations and creative polypharmacy. Antipsychotics are not effective in treating the entire range of symptoms in schizophrenia as well as antidepressants in monotherapy do not cover all aspects of psychopathology in depression. Creative and rational polypharmacy means multiple drug treatment with „only as many drugs as necessary, each for a specific target symptom, each evaluated individually for efficacy and side effects and adjusted optimally, with the elimination of each one that is no longer necessary“ (Joseph 1997). Creative COMBOs provide synergistic benefits and mitigate or eliminate adverse effects by using lower doses of each medication and targeting complementary physiological (compensatory) mechanisms.

TREATMENT RESISTANCE MAY BE AN IATROGENIC TALE – NARRATIVE PERSON-CENTERED CREATIVE PSYCHOPHARMACOTHERAPY MAY SIGNIFICANTLY INCREASE TREATMENT SUCCESS

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

In treating the patient as a person it is essential that we do not forget to treat the person as a patient

MacNaughton 1998

The balance between „treating the patient as a person“ and „treating the person as a patient“ is very important principle of creative, person centered narrative psychopharmacotherapy. The knowledge and practices of clinical psychopharmacology are composed of different stories with different underlying values that can be adapted more or less successfully to the patient's values and preferences (Hamkins 2014). The art of telling, and listening to stories is at heart of what it means to be human, how human beings articulate their experience of the world and make sense of it. „The stories people tell about themselves not only describe themselves but also shape their lives“ (Lewis 2011), in both health and illness. Treatment resistance may arise in part from accumulated negative expectations and by telling destructive, pessimistic or constraining stories, situating the patient in a nowhere-land or in a losing game. Many major mental disorders have an image of the life-long incurable illnesses. Psychiatric patients have been commonly told that „they could not be cured or obtain full recovery and that they would have to take mental health medicines whole life“. Hence, it is quite understandable how treatment resistance in many cases may be a part of an iatrogenic tale.

Creative psychopharmacotherapy is a deeply person-centered practice with highly respectful approach to the patients' individual life stories, values, needs, desires, fears, hopes and dreams (Jakovljevic 2013b, 2015). This concept integrates a variety of efficacious psychotherapeutic and psychopharmacological principles with disorder-relevant psychopathological processes. Basic components of the narrative, person centered psychopharmacotherapy include: 1. the strengths-based building a therapeutic alliance with the patient as a partner; 2. efficacious maintenance of the individually tailored mental health medication; 3. personalized psychoeducation; 4. enhancing personal mastery and creativity; 5. personal recovery orientation and creating new life story. Patients always bring into treatment unique characteristics related to their life stories, vulnerability, resilience and potential for personal growth. Disease has to be cured, but the person of the suffering patient has also to be met, helped and healed. So person-centered psychopharmacotherapy is a personal recovery oriented treatment. Treatment that focusing on recovering only by symptoms elimination and decreasing illness may be like the tail wagging the dog. Patients need to learn specific skills of positive psychology: how to have more positive thinking and emotions, more novelty seeking and engagement, more gratitude, love and sense of life, more accomplishment, and better human relations (see Seligman 2012). That's why person-centered creative psychopharmacotherapy is both illness decrease and wellness increase treatment simultaneously.

Treatment response can be influenced by what a patient «has» (disease), how a patient suffers (illness), how a patient is defined by diagnosis and how community respond to his behavior (sickness, stigma, social role), what a patient «is» (personality, narrative self, human being in the world), what a patient «does» (behaviors, morality), what a patient believes in (life philosophy, spirituality), what a patient feels (life satisfaction, well-being), what a patient «encounters» (life stories) and what a patient tends to be (life management, life script and mission, self-actualization). The narrative psychopharmacology is based on compassionate connection with patients, understanding that human beings live their lives in relationships and connect with one another through the stories they tell (Hamkins 2014) and their life-scripts, life plans made in childhood. Mental health medicaments have both physical and rhetorical effects. In addition to their pharmacodynamic mechanisms, they work also on account of meanings, expectations, and relationships. Treatment response depends on the medicine's biological effects and on the meanings the patient ascribes to the medicine and its effects. Patients come to the clinics with intensely personal life stories of suffering, despair and failure to tell (Lewis 2011) as well as with losing and sorrowful unconscious life scripts. Deconstructing narratives that fuel mental health problems and developing stories of strength and meaning can be cultivated and nurtured into narratives that are resources for personal recovery. Through illness

narratives patients form their own explanations about the causes of their illnesses. Therapeutic narrative refers to explanations how mental health medications work as well as in decisions about using them all the way through therapeutic journey. The restitution narrative presumes the illness to be cured or overcome so that the patient becomes the same or healthy again. While restitution story „yesterday I was healthy, today I am sick, but tomorrow I'll be healthy again“ may work for some illness experience, it can be problematic in the context of some other mental disorders for which cure, or return to previous health as it was once, may not be forthcoming (Frank 1995). So, patients with severe major mental disorders need alternative narrative resources to preserve or reinstate sense of self, meaning, identity, well-being and mental health. In chaos narrative, the illness destroys the life of the patient. The quest narrative is characterized by the patient's search for meaning and the idea that something can be learned or gained from the illness experience (Frank 1995). The recovery narratives involve the four component process: recognizing the problem, transforming the self through recovery narratives, reconciling with the system, and reaching out to others. Establishing a personal relationship with the patient should help the patient to find a new self as a person with a mental disorder who can recover from that disorder with a new perspective on life. Main focus is on the person, not on the symptoms and problems. This approach allows the patient to reconnect with his or her true healthy self. Finding a new, true self is associated with a re-authoring life-story, personal growth, self-actualization and reaching one's full potential. Person-centred psychopharmacotherapy supports self-actualization and self-directed growth focused on patients' strengths and resources. Narrative psychopharmacology combines the resources of reauthoring conversations and mental health medications. The purpose of psychopharmacotherapy is to empower the patients to control their disease, to obtain full personal recovery and to regain control over their life (Slade 2011, Rufener et al. 2015). Psychopharmacotherapy is one essential external support, alongside a whole range of other type of transformation and resilience-promoting supports, skills and strengths. The goals of medication treatment are not only to decrease psychopathology and prevent relapse, but also to improve neuroplasticity and increase wellness helping patients learn new ways of thinking, emotional response and behaviour to get more love, freedom, power, joy and sense of life.

Active participation of patients in their treatment is an essential part of person-centered psychopharmacotherapy. Patients are not just carrier of 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' commit-

ment to treatment goals and continued improvement. According to philosophy of person-centered psychopharmacotherapy patients should be stars of treatment, not a stage for medication trials and errors. Patients should be educated by their psychiatrists regarding optimistic and realistic expectations for the effectiveness of medication therapy and achieving personal recovery. Motivational interview, psychoeducation and informed consent should help patients to experience possible choice of treatment as his/her good choice. Helping patients decide to try mental health medicines and stay on them is an important goal of therapeutic contract. Adherence to a medication regimen is essential for successful pharmacotherapy (Jakovljevic 2014c). The majority of patients who are resistant to treatment, relapsed or rehospitalized are intentionally or unintentionally non-adherent, completely or in some degree. Non-adherence with mental health medicines 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, etc. (see Doran 2003, Haddad et al. 2014, Jakovljevic 2014c). In acute phase of treatment poor adherence to medication regimen increases probability of developing resistant symptoms while in stabilization and maintenance phase increases risk of relapse or new episode. With each new episode of mental disorder the risk of treatment non-response and illness chronicity increases.

The psychology of taking mental health medicines is very complex. 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. 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. These phenomena are universal and of great importance for psychopharmacotherapy and medicine in general. Person-centred psychopharmacotherapy is placebo-response increasing and nocebo-response decreasing oriented practice (Jakovljevic 2014a,b). Any medical or psychosocial treatment has two components, one associated with the specific effects of the treatment itself and the other related to the treatment context and doctor-patient relationship, subjective meaning and personal imagination and expectation. Treatment context and patients’ expectations represent the background of placebo and nocebo responses. The creation of favorable and person-centered therapeutic context may significantly increase placebo and decrease nocebo responses. Some meta-analyses showed that 50 percent of clinical improvement in patients with depression is an effect of placebo, 25 percent is due to pharmacodynamic effects and 25 percent to spontaneous remission (Kirsch et al. 1998,

2008, Benedetti 2011). Maximising therapeutic placebo response and minimizing nocebo response is one of the most efficient and cost-benefit interventions available to physicians (McQueen et al 2013, Jakovljevic 2014a,b).

Person-centred psychopharmacotherapy is patients’ creativity-enhancing treatment (see Jakovljevic 2013c). Creativity has been associated with successful adaptation to daily life and increased well-being (Martin et al. 2015). Creative thinking helps us see an opportunity in every adversity. Research confirmed that creative activities can have a healing and protective effect on mental health and resilience by promoting self-expression, boosting the immune system and reducing distress. Psychiatric medicines may alter, preserve, foster or damage creativity of patients in ways that significantly influence quality of life and personal recovery. Patients often discontinue medication complaining on creativity diminution and cognitive impairments caused by drug treatment. Creativity asserts life, frees the human spirit, improves self-esteem, motivation, self-actualization and achievement and so helps conquer mental disorders. The possible effects of mental health medicines on patients’ creativity are an essential component of a proper medication treatment choice.

CONCLUSION

Mental disorders are still too often chronic, relapsing illnesses. Despite a huge progress in clinical psychopharmacology, the treatment outcome for many psychiatric patients has remained poor. Rates of treatment failure remain high despite the advance of quite a number of new mental health medicines. Better understanding and improvements in preventing and managing treatment unsatisfactory response in current psychiatry are of immense clinical and public health importance. Prevailing unimodal treatment approaches to major mental disorders are not effective and efficient enough in producing remission and personal recovery in a large proportion of psychiatric patients. Creative, person-centered narrative psychopharmacotherapy as transdisciplinary, integrative, multimodal concept may significantly contribute to better treatment effectiveness and efficiency in current psychiatry.

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