

HOW TO INCREASE TREATMENT EFFECTIVENESS AND EFFICIENCY IN PSYCHIATRY: CREATIVE PSYCHOPHARMACOTHERAPY

Part 1: Definition, Fundamental Principles and Higher Effectiveness Polypharmacy

Miro Jakovljević

University Hospital Centre Zagreb, Department of Psychiatry, Zagreb, Croatia

SUMMARY

Psychopharmacotherapy is a fascinating field that can be understood in many different ways. It is both a science and an art of communication with a heavily subjective dimension. The advent of a significant number of the effective and well tolerated mental health medicines during and after 1990s decade of the brain has increased our possibilities to treat major mental disorders in more successful ways with much better treatment outcome including full recovery. However, there is a huge gap between our possibilities for achieving high treatment effectiveness and not satisfying results in day-to-day clinical practice. Creative approach to psychopharmacotherapy could advance everyday clinical practice and bridge the gap. Creative psychopharmacotherapy is a concept that incorporates creativity as its fundamental tool. Creativity involves the intention and ability to transcend limiting traditional ideas, rules, patterns and relationships and to create meaningful new ideas, interpretations, contexts and methods in clinical psychopharmacology.

Key words: *creative psychopharmacotherapy - rational polypharmacy - dysfunction-oriented psychopharmacotherapy - creativity-promoting therapy*

* * * * *

INTRODUCTION

Psychopharmacotherapy is a fascinating field that can be understood in many different ways, with more dogmatism or more creativity in approach. Many people think that psychopharmacotherapy is the most powerful, dominant and effective treatment for mental health problems. It has been advocated as the primary and fundamental form of treatment for all serious mental disorders as schizophrenias, bipolar disorders, depressions, anxiety disorders, obsessive-compulsive disorders, etc. However, mental health medications alone are not sufficient to help people with major mental disorders, but have to be a part of holistic and integrative treatment, as it is, for example, Multidimensional Illness Management and Recovery Program (see Dalum et al. 2011, Slade 2011a). According to the some fervent critics, effectiveness of current psychopharmacotherapy has been exaggerated, the indications widened, and potential risks understated (Slade 2011b). In addition, some people claim that effective treatment in psychiatry is rare and even when it exists, it is not certain that we understand how the treatment works (see Lidskog et al. 2010). Therapeutic changes during psychopharmacotherapy are widely believed to be hard, small, frequently almost imperceptible and very slow. Major causes of this are the unknown etiology of psychiatric diseases and strong stigmatization. Furthermore, diagnoses in psychiatry are usually uncertain and based on a cluster of symptoms. The problem is that one mental disorder may be associated with many different biological mechanisms, and that mental health drugs are not specific diagnosis-related. From perspectives of criticism, psycho-

pharmacotherapy is usually considered to be just a symptomatic treatment, related mainly to placebo response. In addition, psychopharmacotherapy is commonly criticized as unnecessary medicalization of the living problems. Finally, there are also people who think psychopharmacotherapy is a dark art to be feared and despised as a part of toxic psychiatry. Even more, it is a tool for controlling people and their minds by society and institutions.

It is evident that the field of pharmacopsychiatry has expanded significantly during and after the 1990s decade of the brain with a lot of controversial concepts and treatment paradigms, creating both new opportunities and challenges. The advent of a significant number of effective and as well as safe mental health medicines has increased our possibilities to treat major mental disorders in more successful ways with much better treatment outcome including full recovery. However, there is a huge gap between our possibilities for achieving high treatment effectiveness and not satisfying results in clinical practice (Jakovljević 2007). Modern psychopharmacotherapy has claimed itself as scientific, rational, and technical, very much evidence-based. Rational psychopharmacotherapy is often equated with the therapeutic action of mental health medicines on mental disorders in exclusively biological terms. Patients are not rarely treated only as neurobiological objects that respond neurochemically to medications, but not as subjects who respond to the meaning that those medications have (see Mintz 2005). Further, low therapeutic expectations, institutionalized in many ways contribute significantly to poorer treatment outcome. Pessimism and pathologizing bias

are very influential. For example, psychiatric patients have been commonly told that „they could not be cured or obtain full recovery and that they would always have to take mental health medications“. Good news, however, is that there is much room for creativity and improvement in the practice of clinical psychopharmacology (see Niculescu III & Hulvershorn 2010). The concept of creative psychopharmacotherapy could advance everyday clinical practice and bridge the gap by increasing treatment efficiency.

CREATIVE PSYCHOPHARMACOTHERAPY: DEFINITION AND FUNDAMENTAL PRINCIPLES

As an open-ended term creative psychopharmacotherapy may have different meanings for different people. On this occasion it will be enough to outline some basic sketch of what creative psychopharmacotherapy is, and what it is not (see table 1 and 2) because

Table 1. What creative psychopharmacotherapy is

- It is scientific and evidence-based practice and theory with transdisciplinary approach
- It is based on creative, positive, rational and critical thinking
- It is meaning and context-associated practice
- It is an art and practice of the learning organization
- It is an art of healing based on science, experience and relationship
- It is a part of the patient's creativity-enhancing treatment
- It is transculturally sensitive practice
- It is more than Hypocratic psychopharmacology
- It is based on both idiographic and nomothetic knowledge
- It is personalized or person-centered practice, based on shared decision making
- It is individualized and patient preference respecting practice
- It is quality of life, patients satisfaction and personal recovery focused practice
- It is placebo-response increasing and nocebo-response decreasing practice
- It is integrative and holistic practice

the goal of this paper is mainly to commence a professional debate over an important question how to increase treatment efficiency in psychiatry. The concept of creative psychopharmacotherapy refers to an art and practice of mental health drug treatment based on creative psychopharmacology (see Bernstein 1995), learning organization (see Senge 2006), transdisciplinary creative psychology and person-centered psychiatry (see Jakovljević 2007, 2008, 2010). Creativity, on both patients and psychiatrists side, is fundamental tool of this concept and involves the intention and ability to transcend limiting traditional ideas, rules, patterns and

relationships and to create meaningful new ideas, interpretations, contexts and methods in pharmacopsychiatry. Creative thinking refers to the original ideas and mental processes leading to a previously unrecognized opportunity for a solution of the therapeutic problem in a unique, more effective and rapid way (see Jakovljević 2013). Of course, creative thinking may use preexisting objects, information and ideas, but creates a new relationship between elements it uses, for example creating a more favorable treatment context and more effective and safer drug combinations. Finally, creative thinking help us see an opportunity in every adversity.

Table 2. What creative psychopharmacotherapy is not

- It is not quackery practice
- It is not antithesis to modern or postmodern psychiatry
- It is not dogmatic and authoritarian practice
- It is not irrational polypharmacy
- It is not impersonal and only technical practice
- It is not fragmented care/treatment
- It is not marketing based practice
- It is not a random polypharmacy
- It is not adversity increasing polypragmasia
- It is not harmful, toxic or nocebo increasing practice

Treatment outcome depends on a complex interaction of the four groups of factors: 1. Pharmacodynamic and pharmacokinetic factors which influence drug treatment effectiveness via impact on disease mechanisms; 2. Vulnerability factors which enhance the likelihood of disease relapse or recurrence; 3. Resilience and protective factors that enhance the likelihood of recovery from the mental disorder; 4. Generative or creativity factors which increase revelatory learning, resource acquisition and development accentuating personal growth. Consequently, there are multiple and complex factors for psychiatrists to consider in choosing and starting medication as well as in helping patients stay on medication. In addition to more creative use of mental health medications, it is very important to help patients to rediscover their creative confidence. All people seem to be divided into “creatives“ and “non-creatives“ (Kelley & Kelley 2012), and unfortunately too many psychiatric patients are classified into the latter category. Psychopharmacotherapy may alter, preserve, foster or damage creativity in ways that significantly influence quality of life and final treatment outcome.

POLYPHARMACY OF MENTAL HEALTH MEDICATIONS SHOULD BE RATHER A RULE THAN AN EXCEPTION, BUT THERE ARE BIG DIFFERENCES BETWEEN POLYPHARMACIES

Until 1990s polypharmacy within psychiatric community was usually regarded as a bad clinical practice, risky and harmful to the patients. The use of

the two medications from the same class, e.g. two antidepressants, particularly gained bad reputation. Dr. Jonatan Cole (1925-2009) was the first who used the term Creative Psychopharmacology in 1992 referring to “the rational use of multiple medication simultaneously to treat difficult illnesses (Bernstein 1995). According to Bernstein (1995) the concept of creative psychopharmacology refers to 1. Making rational and safe combinations of multiple medications to achieve clinical improvement where simpler regimens have failed, 2. A use of novel drugs or those approved for non-psychiatric indications to treat mood and behavioral disorders, 3. When prescribing drugs thinking more in terms of differential effects of monoamine neurotransmitters and their imbalance on behavior, than in terms of a strict diagnostic categorization. Creative psychopharmacology is not an authorization to practice quackery or to treat patients with alternative remedies without scientific knowledge of rational mechanisms to support the novel therapy (Bernstein 1995).

Synergistic drug combinations (COMBOs) have been promoted by Stahl's Essential Psychopharmacology (Stahl 1996, 2000, 2008, 2013) and by Doran's The Practitioner's Guide: Prescribing Mental Health Medication (Doran 2003). Although today is quite clear that the huge majority of psychiatric patients not only benefit from synergistic COMBOs, as well as that a combined medication treatment may be essential to achieving and maintaining recovery, the most famous treatment guidelines suggest a monotherapy as first choice. Surprisingly enough, one mental health medication is preferable to a combination of medications although there is no one medication covering all symptoms of anyone mental disorder. However, according to the literature the overall prevalence rates of polypharmacy in psychiatry vary between 13%-90% with a continuing debate about its advantages and disadvantages, benefits and risks (Kukreja 2013).

In clinical practice it is very difficult to achieve a full remission or recovery with monotherapy, so polypharmacy of mental health medications should be rather a rule than an exception. Good clinicians practice rational polypharmacotherapy, and those who do it expertly are leaders in their field (Doran 2003). The true polypharmacy (see Ghaemi 2001) or creative polypharmacotherapy is the skillful and rational combination of mental health medications. 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 and rapidly or achieve a full recovery when treated with a combination of mood stabilizers from different drug families. A common example of monotherapy in effectiveness may

be seen in bipolar depressed patients, when 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 medications 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 response only partially, while treated with a single high potent benzodiazepine may have breakthrough depressive symptoms or breakthrough panic attacks (see Doran 2003). COMBOs with these two classes of drugs together may eliminate both depression and panic attacks. In general, creative COMBOs with an additional, synergistic therapeutic effect between two or more medications make the overall treatment benefit greater than that achieved by either of the medications alone. Patients with panic disorder, for example, respond better and sooner to an antidepressant and a high potent benzodiazepine COMBO, than to either of these medications alone. When panic attacks disappear soon, the benzodiazepine is excluded carefully, 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 a complete remission is very important goal and principle 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 (Jakovljević 2005). 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). Combined medications should be provide synergistic benefits and mitigate or eliminate adverse effects by using lower doses of each medication and targeting complementary physiological (compensatory) mechanisms (Niculescu III & Hulvershorn 2010).

Creative psychopharmacotherapy is disease mechanisms oriented and treatment goals directed

Creative psychopharmacotherapy is disease mechanisms/processes directed, not on particular diagnosis focused practice. The madness of King George is an extreme, but educative, example of how not-knowing of

the underlying disease (porphyria) mechanism can result in treatment failure and lead to considerably more health risk than benefit. In creative approach to psychopharmacotherapy it is essential to target specific symptoms that may serve for the underlying psychopathology (Janicak et al. 2006). It is very important that treatment cover all important symptoms such as reality distortion, social withdrawal, mental disorganization, sleep disorders (insomnia, hypersomnia), anorexia, bulimia, sexual disturbances, depression, euphoria, mood bipolarity, impulsivity, obsessivity, compulsivity, aggressivity, suicidality, fear, anxiety, etc. “Deficient mesocortical dopaminergic function may be operative in generating inertia and behavioral retardation, since this transmitter appears to be important in governing goal directed behavior. The hyperactivity of mesolimbic dopaminergic system in psychosis is associated with attributing more salient meanings to external stimuli and internal representations, while antipsychotics dampen the process of aberrant salience attribution through anti-dopaminergic impact. Noradrenergic deficiency may be seen as underlying anhedonia, therefore restoring adequate functional levels of this transmitter may result in reawakening the depressed patient's ability to experience pleasure. Serotonin, on the other hand, may partially function as a regulator of mood, aggression, and anxiety“ (Bernstein 1995) so that low brain 5-HT may render individuals vulnerable for displaying violent aggression, anxiety and depressive disorders, depending on their life contexts. This approach is very similar to the concept of functional psychopharmacology and a goal-directed, dysfunction oriented psychopharmacotherapy (van Praag 1993).

PRIMACY OF PATIENT WELFARE IS FUNDAMENTAL PRINCIPLE OF CREATIVE PSYCHOPHARMACOTHERAPY

According to The Physicians Charter, the primacy of patients welfare is one of the three fundamental principles of professionalism in medicine (Jakovljević & Ostojić 2013) whereas the risk-benefit evaluation is one of the basic tenets when planning a treatment strategy. Assessment of psychic, neurologic and somatic status as well as recognition of contraindications for individual medications is of a huge importance. Cardinal principle is: “*primum non nocere*“ – “first of all do not harm“ (Hypocrates rule), and treatment benefit must significantly overcome treatment risks. It is obligatory to watch carefully for the appearance of adverse events through entire course of psychopharmacotherapy as well as to respond promptly and suitably. According to Holmes’ rule (1861), “medications are guilty until proven innocent” (see Ghaemi 2001). All medications may be toxic. It is only the indication and the dosing that makes them effective with a careful risk-benefit evaluation. Creative combinations of various medications include therapeutic synergism with better treatment tolerability and safety (Jakovljević 2010)

Appropriate medications should be applied in every phase of treatment

Mental health medications can be used for multiple purposes, and the choice of medications depends on the goal of the treatment. We can identify three broad categories of goals for mental health medication treatment: acute phase treatment goals, stabilization phase goals and maintenance or prophylactic treatment goals. Different mental health medications fit different phases of psychopharmacotherapy. Some medications are quite appropriate for application in an acute phase of treatment, but not in maintenance or prophylactic treatment phase. Vice versa is also true: certain medications are not so effective in acute phase, but are exceptionally beneficial when applied in maintenance or prophylactic treatment phase (see Janicak et al. 2006). At each phase of treatment it is very important to select the primary treatment perspective that best fit the patient (see Jakovljević 2008).

Careful monitoring over the entire course of treatment

It is necessary to continually look for further possible improvement of the patient's well-being. Careful monitoring of treatment adherence and patient's commitment to treatment goals as well as of possible development of medication tolerance is very important. Good adherence with drug treatments is associated with better-tailored treatments that lead to more satisfied and insightful patients and to fewer undesirable side-effects and better treatment acceptability by the patients. Finally, continual monitoring of the presence or absence of all important symptoms and specific problems is needed over entire course of treatment.

Creative psychopharmacotherapy is strictly individualized

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. Although this field heralds great promise for individualized patient healthcare, there is only a few reliable markers in clinical practice. When starting with psychopharmacotherapy, it is important to choose medications that 1. can treat comorbid conditions present, 2. haveno a particular side-effect, 3. do not complicate a medical condition, 4. have no an interaction with another medications, 5. have side-effect 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). It is important to note that the overlap between comorbid disorders and their possible interdependence may afford parsimony in the number of medications used (Niculescu III & Hulvershorn 2010). It is always useful to have in mind that good physicians treat diseases, while great physicians treat individuals with diseases.

CONCLUSIONS

With a more creative and rational use of available mental health drugs, it is possible to achieve a better treatment efficiency in psychiatry and bridge the gap between good therapeutic possibilities and unsatisfying results in day-to-day clinical practice. Creative polypharmacotherapy is the skillful and rational combination of mental health medications. Different mental health medications fit different phases of psychopharmacotherapy. At each phase of treatment it is very important to select the primary treatment perspective that best fits the patient.

Acknowledgements: None.

Conflict of interest : None to declare.

References

1. Bernstein JG: *Drug Therapy in Psychiatry*. Third edition Mosby, 1995.
2. Doran CM: *Prescribing Mental Health Medication – The Practitioner's Guide*. Routledge, London & New York, 2003.
3. Ghaemi SN: "All the worse for the fishes": Conceptual and historical background of polypharmacy in psychiatry. In Ghaemi SN (ed): *Polipharmacy in Psychiatry*, 1-34. Marcel Dekker, Inc., New York & Basel, 2001.
4. Jakovljević M: Creativity, mental disorders and their treatment: Recovery-oriented psychopharmacotherapy. *Psychiatr Danub* 2013, 25:311-315.
5. Jakovljević M & Ostojić Lj: Professionalism in contemporary medicine: If it is an important academic issue, then surely it is a "hot" issue as well. *Medicina Academica Mostariensia* 2013; 1; 6-17. *Psychiatr Danub* 2013; 25(suppl 1):6-17.
6. Jakovljević M: Transdisciplinary holistic integrative psychiatry – A wishful thinking or reality? *Psychiatr Danub* 2008; 20:341-348.
7. Jakovljević M: Contemporary psychopharmacotherapy in the context of brave new psychiatry, well-being therapy and life coaching. *Psychiatr Danub* 2007; 19:195-201.
8. Jakovljević M: Modern psychopharmacotherapy and new concepts of treatment: From treatment nihilism to treatment renaissance and complete reintegration. *Psychiatr Danub* 2005; 17:243-245.
9. Jakovljević M: The decade of the brain in biological psychiatry – Biological psychiatry between conservation and change. *Psychiatr Danub* 1995; 7:75-87
10. Janicak PG, Davis JM, Preskorn SH, Ayd FJ, Marder SR & Pavuluri MN: *Principles and Practice of Psychopharmacotherapy*. Fourth edition. Lippincott Williams & Wilkins, 2006.
11. Joseph S: *Symptom-Focused Psychiatric Drug Therapy for Managed Care*. The Haworth Medical Press, New York & London, 1997.
12. Kelley T & Kelley D: Reclaim your creative confidence. *Harv Bus Rev* 2012; 90:1115-118.
13. Kukreja S, Kaira G, Shah N & Shrivastava A: Polypharmacy in Psychiatry: A review. *Mens Sana Monogr*. 2013;11:82-89. Doi:10.4103/0973-1229.104497
14. Lidskog M, Halnes G, Oliveira RF, Kataleski JH & Blackwell KT: Biochemical networks in Psychiatric Disease. In Tretter F, Gebicke-Haerter PJ, Mendoza ER & Winterer G (eds): *Systems Biology in Psychiatric Research – From High-Throughput Data to Mathematical Modeling*, 301-320. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2010.
15. Mintz DL: Teaching the prescriber's role: The psychology of psychopharmacology. *Academic Psychiatry* 2005; 29:187-194.
16. Niculescu III AB & Hulvershorn LA: Toward early, personalized, rational polypharmacy in psychiatry: A tridimensional approach. *Psychopharm Review* 2010; 45:9-16.
17. Senge PM: *The Fifth Discipline – The Art & Practice of the Learning Organisation*, Random House, London, 2006.
18. Slade M: Effectiveness rationale. In Slade M: *Personal Recovery and Mental Illness – A Guide for Mental Health Professionals*, 63-68. Cambridge University Press, 2011.a
19. Slade M: The contribution of medication to recovery. In Slade M: *Personal Recovery and Mental Illness – A Guide for Mental Health Professionals*, 172-175. Cambridge University Press, 2011.b
20. Stahl SM. *Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press, 1996.
21. Stahl SM: *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Fourth Edition. Cambridge university Press, 2013.
22. Van Praag HM: „Make-Believes“ in Psychiatry or Perilsof Progress. Brunner/Mazel Publishers, New York, 1993.

Correspondence:

Prof. dr. Miro Jakovljević, MD, PhD
University Hospital Centre Zagreb, Department of Psychiatry
Kišpatićeva 12, 10000 Zagreb, Croatia
E-mail: predstojnik_psi@kbc-zagreb.hr