

CREATIVITY IN PSYCHOPHARMACOTHERAPY - THE BRIGHT SIDE OF FACE OF PSYCHIATRIC GOD JANUS

Aleksandar Damjanović

School of Medicine, University of Belgrade, Clinic for Psychiatry, Clinical Centre of Serbia, Belgrade, Serbia

SUMMARY

This paper discusses about challenges to psychopharmacotherapy, evidence-based psychopharmacology, creative psychopharmacology, creativity and dopamine, creative-rational polypharmacy as a paradigm for creativity in psychopharmacotherapy, and about polypharmacy classification as a good, bad and ugly

By stimulating the patient to participate in the creative and artistic process we effect on his optimal identification with the role of the sick person. Through creation, imagination and visualization patients can recognize their own reservoir of inner healing and create a healthier new identity. Psychopharmacotherapy can prevent the deterioration of creativity affecting the quality of life and personal recovery. It may also affect the goals and aspirations of patients as well as the way in forming strategies of their realization.

Key words: pharmacotherapy – polypharmacy – creativity - dopamine

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INTRODUCTION

I wouldn't have had such good scientific ideas if I had thought more normally.

John Nesh

In an editorial in the well known, British Journal of Psychiatry, Paul Harisson and several world leading psychopharmacologist emphasize the necessity of psychotropic medication in psychiatric clinical practice. They point out that it is necessary to revitalize the importance of psychopharmacs, especially of their efficacy and tolerability. The authors of this text consider that the prominence of psychopharmacology, with respect to other psychiatric clinical methods of treatment, will ensure and strengthen the role of psychiatry as a medical discipline in the future (Harisson et al. 2011). The challenges ahead pharmacotherapy are numerous- they do not come only from the phenomenon of resistance to therapy, toxic effects, lack of response, partial response, they are also the resultant of mental models, visions, personal skills of therapist and the patient, as well as macro-influences of family environment of the patient as well as the expectations of society in general. However, new trends are becoming dominant in striving for optimal pharmacotherapy position. It is certainly a change in the philosophical approach to treatment- introduction of polypharmacy as legitimate method with all its advantages and disadvantages. The fact is that psychiatric medication changes neurochemical systems in the brain- therefore, therapy does not treat specific disease. Concept "One diagnostic category one class of pharmaceuticals" (with the exception of lithium) is not longer valid. Today it is increasingly present dominance of rational combination of psychopharmacs so-called COMBO strategy (Synergistic drug combination). Of course, all of these perturbations initiate a certain moral-ethical and philosophical questions. Moral philosophy

of pharmacotherapy is inevitable in relation to security, tolerability and adherence (acceptability) of given medication with respect to each patient individually. The fundamental question refers to consideration of the patient's optimal (best) interest, cost of treatment, risk-benefit ratio and the patient's preferences in respect to the indicated treatment.

A special chapter in the modern principles and methodology of assessment of the functioning psychopharmacs is a concept of evidence-based medicine which is based on a meta-analysis a whole range of valid, primarily double-blind studies respectively RCT (randomized clinical trial). So-called Algorithms, guidelines for good clinical practice are constructed based on the evaluation of these studies. They are based (algorithms) on a specific philosophy that consider- that purpose of the treatment should be remission and that first choice of treatment should be the one that gives optimum efficiency or safety. Algorithms give priority to the simplest interventions (Occam's razor), where each of the following intervention actually lead to increased complexity and a higher risk. Multiple options are considered when they are meaningful and necessary, and in addition, it is necessary to respect the views of the patient. Of course, it immediately became clear that such guides and algorithms have many shortcomings. Psychiatrists often do not want to follow them „blindly“, many of them have „developed their own algorithms“, often have a certain "dark stain" with respect to the legal use of for them rigid treatment systems. A long time ago, Bleuer talked about autistic, "undisciplined" characteristics of psychiatrists opinions. Therefore, is there an optimal solution? Ultimately, whether is it psychopharmacotherapy art, or some kind of cookbook, with a series of distinct and (pseudo) original recipes? All this, complicates the implementation of official guides whether it is on Serbia, Croatia or in neighboring countries.

However, it seems that the paradigmatic study of Steinart, who asked his colleagues quite a simple question, but with a series of moral, bioethical and professional connotations- consequences: What neuroleptic would you give to yourself or family member in the case of schizophrenia? The survey results were very similar to those officially recommended medication from official guide and algorithms- olanzapin, risperidon, quetiapine, amisulprid (Steinart 2003). Contrary to this study, a year later, american authors, using logistic regression, analyze the therapeutic decision of 100 psychiatrists who treat 200 patients. A number of factors influenced the choice between typical and atypical antipsychotics. However it is interesting that *doctors age represents the strongest predictor for choice of antipsychotic drugs!!! Doctors older than 50 years, five times more prescribed typical antipsychotics* (Hamann et al. 2004). After these two studies, really raises the ethical question- what guide our decisions in the choice of therapy: subjectivity, objectivity, laziness, inertia, stubbornness, discrimination, (pseudo) subjective-objective decision etc.

Is there a universal decision principle? Does subjectively can be translated into optimal (biological) or creative decision?

The biological bases of mind is based on personalized (individual) brain which driven by unique experience creates a unique dynamic configuration of neural compounds. This neurophilosophical principle to some extent facilitate adoption of critical decision (largely dictated by Kant's Critique of Practical Reason) which refers to clinical implementation of pharmacotherapy whose substantive decision should be individuality and creativity.

Dr. Jonathan Cole (1925-2009) is the creator of the concept of creative psychopharmacology, which now, Professor Miro Jakovljevic especially extends, optimize and creatively modify. From Cole's original definitions we can extract characteristics of creative psychopharmacology (hereinafter referred to as CP):

- Rational and safe combinations of medications used for the treatment of mentally ill;
- Using the new pharmaceuticals or those that have been approved for non psychiatric indications in the treatment of behavioral disorders or mood disorders;
- When using some treatment, then we have to think about the different effects on neurotransmitters and their consecutive imbalance within the different modalities of behavior;
- CP is not an authorized practice of quackery or treatment of patients with alternative methods without scientific support or knowledge of the rational mechanisms that support new therapy.

Jakovljevic in a series of papers completed and plausible evolving concept of CP (Jakovljevic 2009a, 2009b, 2008, 2007, 2005, 1995). Here are some of his observations and general reviews that reinforce the fundamentals of CP:

- CP is the only cornerstone holistic and integrative treatment of mental illness;
- CP is always highly personalized;
- It is also strictly individualized;
- CP is directly directed to psychopathological mechanisms or processes and is not particularly oriented to a diagnostic practice;
- CP is context dependent practice;
- Suitable medication can be applied in any stage of the treatment;
- It is urgently required to achieve complete remission;
- Cautious monitoring during the entire treatment.

CONCEPT OF CREATIVITY

The concept of creativity is refracted through the power of improvisation, intelligence, mystery, through the rational use of the mind, spirit, fantasy, the ability to control internal forces, directing impulsiveness towards the islands of coherence. However, if we try to deconstruct the demons of creativity then it means the possibility of using simplified material to make something new, different, usually more complex. In terms of syntax and language, that means of limited vocabulary to make an endless set of dialogue always new, flexible, diversified. Homer, Dante, Cervantes, Shakespeare, Moliere, Bukowski, Fante are always created an abundance and continuum of new mindsets. At the behavioral level creativity is characterized by ever new sequences of actions. Despite the fact that spirituality represents the substrate of creativity which at first sight essentially define this phenomenon, it is clear that certain elements of neuro biological define the mystery of creativity.

NEUROSCIENCE OF CREATIVITY

The role of dopamine (hereinafter referred to as DO) shows a significant participation in the phenomenon of creativity. Of particular importance is that this transmitter shows a different representation in certain regions of the brain which from a neuroscientific or neuropsychological aspect significantly modulate creativity (prefrontal lobe, basal ganglia, n. Accumbens, etc.). It is interesting that people with creative experience have a very high degree of electrical activity (very high arousal) when they find a solution for complex intellectual and speculative problems and in these situations registered significant changes in the status of DO. It is possible that disinhibition of DO system leads to significantly increased expression of grandiosity, insight, excitement and intensity of emotional discharge which represents the first phase of creativity. Afterwards, when it comes to the exhaustion of the system and depletion of DO, it occurs despondency, which can lead to depression, perfectionism, strengthening the criticality and strengthening of evaluation power which leads to the second stage creative productivity. One of the key structures in neuropsychological function of the brain is prefrontal

cortex (hereinafter referred to as PFC). How does the activity of PFC may affect the fluctuations of DO? In the case of reduced PFC activity occurs- strengthening the emotional component, sensory, dominating a sense of here and now, dominating influence of the environment, reducing the sense of self, conditions specific to infants and children, losing the sense of space and time. This condition is characterized by *excess of DO*. In the case of PFC activation there is a dominance of cognitive processes, hierarchy of past-present-fantasy, perception of internalized dominant, „personalized meaning“, a strong sense of self, clear definitions of space-time categories which is specific for older children, adolescents and adults and is the result of reduced levels of DO. The system of DO neurons has beginning in limbic regions of the brain stem and from there is projected to motivational regions of the frontal cortex. The system is associated with reward, positive mood and satisfaction. It is also included in the process of searching for new, impulsiveness, psychoticism and addiction. Hence follows a series of hypotheses regarding the role of DO:

- The hypothesis of anhedonia;
- Predicting the error (learning, action selection);
- Salience- attention;
- Incentive salience;
- Uncertainty- suspense;
- Assessment of cost-benefit;
- Energizing-motivating behavior.

MENTAL DISORDERS AND CREATIVITY

Many years of research have shown that mental disorders are associated with positive psychological characteristics of creativity, spirituality and resilience. Unfortunately, these positive aspects are underestimated as a potential benefit of the mentally ill (Galvez 2011). It has been shown that highly creative people are at greater risk for certain forms of psychopathology including mood disorders, schizophrenia spectrum disorders and alcoholism. People with creative professions are often treated by mental disorders than the general population (Kyaga 2011).

CREATIVE THINKING AND PHARMACOTHERAPY

Creative thinking can refer to the pre-existing objects, information and ideas. But when we create new relations between the elements that we use in therapy for example, we are able to establish a favoring context treatment which implies plausible but also an objective relationship between the efficacy and safety of medications. Creative thinking helps us to see opportunism in each diversity and consecutively to create a new, better context. Creative psychopharmacotherapy is a new concept which incorporates creativity both psychiatrist and patient as a fundamental communication tool. Patients with bipolar disorder and schizophrenia often

complain and terminate therapy because of the creative and cognitive decline caused by pharmacotherapeutic treatment. Of course that treatment of patients can be roughly divided into creative-promoting but also creative-inhibiting ("creative killing"). Creative promoting treatment involves stimulation of patient to learn and uses the creative modes of thinking and behavior that directs their interests in creative fields of functioning. Creative expression may be an important contribution to the treatment and healing process (Suckey & Nobel 2010). By stimulating the patient to participate in creative and artistic processes we effect on his optimal identification with the role of a sick person. Through creation, imagination and visualization patients can recognize their own inner healing reservoir and to create a healthier new identity. Psychopharmacotherapy may also prevent deterioration of creativity affecting the quality of life and personal recovery. Medication in the field of mental health has an impact on cognition, mood and emotion, motivation, and behavior. It can cause subjective changes in patients, way of understanding things, interpret reality, way of perceiving themselves and others as well as their fantasy impressions. Pharmacotherapy may also affect the goals and aspirations of patients as well as the way in forming strategies to realize them (Murawiec 2009).

RATIONAL POLYPHARMACY AS A PARADIGM OF CREATIVITY IN PSYCHOPHARMACOTHERAPY

Polypharmacy relates to the use of two or more pharmaceuticals in the treatment of the same condition, use of two or more drugs of the same chemical classification, or use of two or more drugs of the same or similar pharmacological activity for the treatment of various conditions.

Modern classification of polypharmacy among other includes the following classification (NASMHPD 2001):

- **Same-Class Polypharmacy.** The use of more than one medication from the same medication class (e.g. two selective serotonin reuptake inhibitors, such as fluoxetine plus paroxetine).
- **Multi-Class Polypharmacy.** The use of full therapeutic doses of more than one medication from different medication classes for the same symptom cluster (e.g. the use of lithium along with an atypical antipsychotic, such as fluoxetine plus olanzapine for treatment of mania).
- **Adjunctive Polypharmacy.** The use of one medication to treat the side effects or secondary symptoms of another medication from a different medication class (e.g. the use of trazadone along with bupropion for insomnia).
- **Augmentation.** The use of one medication at a lower than normal dose along with another medication from a different medication class at its full therapeutic dose, for the same symptom cluster

(e.g. the addition of a low dose of haloperidol in a patient with a partial response to risperidone) or the addition of a medication that would not be used alone for the same symptom cluster (e.g. the addition of lithium in a person with major depression who is currently taking an antidepressant).

- **Total Polypharmacy.** The total count of medications used in a patient, or total drug load. Consideration of total polypharmacy should include prescription medications, over-the counter medications, alternative medical therapies, and elicit pharmacological agents.

SPECIFICS OF POLYPHARMACY

Kukra et al. (2013) state that the rate of polypharmacy in psychiatry varies between 13-90%. Rittmannsberger et al. (2004) found that monotherapy in psychiatric patients in 1980 was 48%, while in the period of 1981-1990 is lowered to 31%, and between 1991-2000 to 20%.

From the socio-demographic factors should be mentioned that polypharmacy is more widespread in the male population. Antidepressants and antipsychotics are commonly prescribed as co-medication with a basic therapy of ADHD, while according to ICD 10 polypharmacy is most common in schizophrenia, schizotypal and delusional disorders (De las Cuevas & Sanz 2004).

In geriatric population, polypharmacy is the rule rather than the exception. In people over 65 years, over 90% receive at least one medication per week, more than 57% receive over 5 medication per week and more than 12% over 9 medication. Cohort study that compare the use of medications in the elderly population showed that between 54% -67% of people older than 65 years take more than 5 medications. Beers criteria provide a list of medications that should be avoided in the elderly population. (Bryan et al. 2007).

This raises the logical question whether the polypharmacy is a need? Stahl's Essential Psycho-pharmacology (2005) & Doran's The Practitioner's Guide (2003) promote a synergistic combination of psychopharmacs. Most psychiatric patients has benefited from the synergism of drugs and they are also essential for achieving and maintaining recovery. In clinical practice it is very difficult to expect to achieve full remission or recovery only with monotherapy. Therefore, polypharmacy of psychotropic medication should be rather the rule than the exception. (Jakovljevic 2013).

"Alibi" reasons for poly-pharmacotherapy is primarily related:

- On treatment of two pathophysiologically distinct but comorbidity disease in the same patient (eg, a patient with Parkinson's disease and psychosis);
- Treatment of side effects caused by primary drug (haloperidol and antiparkinsonian);
- To enable the improvement while waiting for the delayed effect of another medication (antidepressant plus benzodiazepines);

- In order to treat superimposed stages of the primary disorder (in the treatment of post-psychotic depression);
- To enhance the effect of augmentation in primary treatment (antidepressants plus L-methylfolate, antipsychotic plus antidepressant in schizophrenia (Preskorn 2007).

The irrational polypharmacy represents the opposite of rational, arises from the fear of clinicians due to poor and unstable condition of the patient, sloppy diagnosis, improper titration pharmaceuticals, absenteeism compliance, disregard instructions from the guide, inadequate knowledge of receptor pharmacology or simply not paying attention to it (Kingsbury 2001).

Naser Gaem (2001) is the creator of the concept of rational/creative polypharmacy which involves the skills of rational combining of psychopharmacs. According to his doctrine it is combination of pharmaceuticals with the synergistic action, as the use of multiple medications when each of them effect on specific target symptoms. The evaluation of each medication is individual and implies optimum efficiency assessment and side effects for every medication. It is necessary to eliminate some psychopharmacs when it is no longer needed in treatment (Jakovljevic 2013).

In practice, most often encountered are following types of polypharmacy:

- Aripiprazole + haloperidol for psychosis;
- Valproic acid + lamotrigine for mood stabilization;
- Same chemical class to treat separate conditions Clonazepam for anxiety + temazepam for sleep;
- Risperidone for psychosis + low-dose quetiapine for anxiety;
- Same pharmacological action to treat the same condition Diphenhydramine + temazepam for sleep;
- SSRI + nortriptyline for depression.

Also, interesting is the next "movie" classification of polypharmacy types (Kingsbury & Lotito 2007):

- GOOD;
- BAD;
- UGLY.

Good polypharmacy

- Lithium or valproate + risperidone, olanzapine, or quetiapine for bipolar mania;
- Clozapine + risperidone for treatment-resistant schizophrenia;
- Lithium or valproate + ziprasidone or aripiprazole for bipolar mania;
- SSRI + mirtazepine for posttraumatic stress disorder;
- Clozapine + haloperidol for treatment-resistant schizophrenia.

Two polyfarmacy strategies can be considered as good. In the first case of good polypharmacy a combination of the two drugs, based on research, shows that

combination is significantly effective in comparison to single use. Since these studies were of relatively short duration, the other strategy of rational polypharmacy would relate to combined extrapolation of pharmacodynamics of concomitant medication from the existing research results, expert opinion or hypothesis. It is also certain that the largest number of research studies supports polypharmacy with manic episodes within bipolar disorder. Field of schizophrenia requires monitoring in cases of polypharmacy because of the small number of studies that are quite contradictory. For instance, although there are case studies suggesting that adding risperidone may enhance defense response to clozapine, double-blind studies of this combination have contradictory results. Knowledge of the disorder biology and pharmacodynamic properties of medications, represent the basis of a rational poly-pharmacotherapy. Adding bupropion which has the blockade of noradrenaline and DO uptake to SSRI, may be rational in the treatment of depression, although lacks a double-blind placebo-controlled studies which can confirm this combination as effective.

Bad polypharmacy

- SSRI + venlafaxine for depression;
- Aripiprazole (at suboptimal dosing) for mania + quetiapine (low-dose) for sleep;
- Lithium (at suboptimal dosing) + gabapentin for mood stabilization;
- Citalopram + paroxetine (both at suboptimal doses) for depression;
- Donepezil for dementia + oxybutynin for incontinence.

Bad polypharmacy relates to a combination of two or more medications where we do not pay attention to the pharmacodynamic characteristics of drugs. Reasons for bad polypharmacy are numerous:

- One of them is the fear of clinicians that will "rock the boat", so they restrain from any discontinuation of the current medication, which are actually partially effective.
- Adding some pharmacological is actually an attempt to achieve a full therapeutic effect. In such a case, additional medications may be sufficient as monotherapy, which means that exclusion of medication might be more adequate than a combined approach.
- The next reason for bad polypharmacy deserves mention: following the temporary caprice (fashion). For example, in practice, we often meet adding a small doses of quetiapine for sleeping to a sub-optimal doses of mood stabilizers or antipsychotics. Although this "maneuver" is clearly expensive, it remains unclear why would adding a lower dose of quetiapine allow greater benefit than a pure anti-histamine agent.

- One of the most common reasons for poor polypharmacy is combining the pharmacodynamic properties of medications. For instance, the use of two SSRIs, both in suboptimal doses. Next is addition of serotonin noradrenaline reuptake inhibitors (SNRI) such as venlafaxine to SSRI, wherein inhibition of serotonin reuptake by SSRI might be quite enough.

Ugly polypharmacy

- Fluoxetine + amitriptyline for depression;
- Valproic acid for mood stabilization + antiretroviral for HIV infection;
- Olanzapine for psychosis+ low-dose mirtazapine for sleep + valproic acid for seizures;
- SSRI for depression + tramadol for pain.

In contrast to polypharmacy, which is primarily ineffective or wasteful, "ugly" polypharmacy might be harmful. Two big mistakes can lead to damaging outcome:

- Ignoring the pharmacokinetic interaction;
- Ignoring the profile of side effects of combining medications. As the simplest example, although a potent inhibition of CYP450 paroxetine and fluoxetine is known, typically little attention is paid to drug metabolism which are combined with the SSRI. Lack of attention in providing multiple medications with similar side effects can lead to numerous complications. For example, many psychiatric drugs can lead to increased body weight. However, several of these medications are often freely combined without considering alternatives that are neutral in relation to the body weight.

HOW TO COPE WITH BAD AND UGLY POLYPHARMACY

Clinicians who prescribe psychiatric medication must be aware of the existence of a high prevalence of polypharmacy. Despite all the shortcomings polypharmacy may be necessary, especially with comorbidity or when monotherapy is not sufficient to provide adequate stability i.e. improving the mental condition of the patient. One can deal with polypharmacy with SAIL and TIDE approaches: SAIL means: Simple drug regimen, Adverse effects knowledge, clear Indication, keep List of drug name and dosage in patient's chart. TIDE means: Allow Time to address medication issues, understand Individual variability, avoid potential dangerous Drug-drug interactions, and Educate patients regarding treatment (Kukra et al 2013).

Instead of a Conclusion - Creativity and polypharmacy - Strategy for the Future

Rational-creative psychopharmacotherapy represents form of a new, brave, proactive- evolutionary area of modern psychiatry. Referring to rational-creative form of polypharmacotherapy, we believe that this treatment

will lead to the discovery and development of target specific neuroreceptors that would be associated with a reduction of residual-secular-resistant manifestations of mental illnesses that represent a major challenge in treatment. Finding psychopharmac, or more of them, with targeted model of action is possible, and gives hope that we will be able to treat severe challenges such as negative symptoms of schizophrenia, suicidal tendencies in depressed, anhedonia and cognitive deficits which become inseparably-interfering part of nearly every mental illness.

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Correspondence:

Professor Aleksandar Damjanovic, MD, PhD
Neuropsychiatrist Clinic for Psychiatry, Clinical Center of Serbia, University of Belgrade
Pasterova 2, 11000 Belgrade, Serbia
E-mail: damal64@yahoo.com