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NEW GENERATION VS. FIRST GENERATION ANTIPSYCHOTICS DEBATE: PRAGMATIC CLINICAL TRIALS AND PRACTICE-BASED EVIDENCE

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SUMMARY

There has been significant confusion about the relative advantage of new generation antipsychotics over first generation antipsychotics as well as of clinical trials performed to evaluate their efficacy vs. those designed to evaluate their effectiveness. Pragmatic or effectiveness clinical trials like CATIE and CUtLASS sponsored by governments have challenged the current worldview of the greater advantages of new generation over first generation antipsychotics and suggested more clinical applicability of older antipsychotics. Public policy regarding the role and place of modern antipsychotics in schizophrenia treatment is usually guided by the imperfect state of clinical trials and by economic constraints. The right question is not whether new generation antipsychotics are better than first generation antipsychotics in terms of effectiveness, tolerability and safety. How to reach personalized , evidence based and value oriented decision making in the complex treatment of schizophrenia and other psychotic disorders, that is the question now. Personalized medicine in psychiatry is not possible without the availability of enough number of different modern antipsychotics.

Key words: *antipsychotics – effectiveness - clinical trials - personalized medicine*

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INTRODUCTION

The introduction of the third generation antipsychotics (TGAs) in clinical practice during1990s has largely increased the range of pharmacotherapeutic options for patients with schizophrenia, their families and clinicians as well as the expectations from psychopharmacotherapy of this devastating disease. Over the course of the last decade, TGAs have become the standard of antipsychotic pharmacotherapy and the first line treatment for schizophrenia (Sartorius et al. 2003, Tandon & Fleischhacker 2005). Each pharmaceutical company that markets a new antipsychotic has supported numerous RCTs in an attempt to demonstrate the superiority or some advantages of its medication compared with its competitors. However, the results of randomized controlled clinical trials (RCTs), pragmatic clinical trials (PCTs), meta-analyses and systematic reviews have delivered inconsistent, discrepant, opposite and controversial messages about comparative efficacy and effectiveness of the new generation antipsychotics (TGAs). Given the fact that results of RCTs and PCTs conflict and contradict each other, it currently seems that the RCTs and PCTs compete for supremacy. This competition raises a series of epistemiological, conceptual, explanatory and moral/ethical questions making a scientific crisis in contemporary psychiatry. Significant confusion about the relative value of TGAs as well as of clinical trials performed to investigate their efficacy (RCTs) vs. those designed to investigate their effectiveness (PCTs) prevails in literature (Fleischhacker WW & Goodwin 2009).

NEW GENERATION VS. FIRST GENERATION ANTIPSYCHOTICS DEBATE

There has been a thorny debate about superior efficacy of new generation antipsychotics (see Fleischhacker & Goodwin 2009, Leucht et al. 2007, Geddes et al. 2000). The RCTs have been claimed for a long time to be the cornerstone of the evidence-based treatment and the «gold standard» for evaluating efficacy and effectiveness of antipsychotics. Generally, RCTs have shown that

modern antipsychotics (TGAs) are at least as effective as the conventional antipsychotics (FGAs) in the treatment of positive symptoms, but superior in the treatment of some specific symptoms, like negative symptoms, mood symptoms and cognitive symptoms as well as in maintaining or enhancing quality of life with significantly less extrapiramidal side-effects (Emsley & Oosthuizen 2005). On the RCTs taken together, so called «atypical antipsychotics» (excluding clozapine) should be the first-line treatment agents for schizophrenia (Emsley & Oosthuizen 2005). Since recently, RCTs have been criticized to produce artificial results not reflecting the «real world» conditions. PCTs or so called «real world» studies on antipsychotics have been usually claimed to give more reliable data on the effectiveness of antipsychotics (efficacy, safety and tolerability, patient functioning, and acceptability) in comparison to RCTs. However, PCTs have also delivered discrepant and conflicting results that are used in different ways with different messages.

PRAGMATIC TRIALS: STEP FORWARD OR A CONUNDRUM?

Results of some PCTs, but government-sponsored studies in the United States and the United Kingdom, have challenged the prevailing worldview of the greater effectiveness of TGAs over FGAs and are reinvigorating interest in the utility and applicability of FGAs (Nasrallah & Tandon 2009).

The CATIE (Clinical Antipsychotic Trials in Intervention Effectiveness) study, sponsored by the US National Institute of Mental Health (NIMH), found that the first generation antipsychotic (FGA) performed very well against the third generation antipsychotics (TGAs) risperidone, olanzapine, quetiapine and ziprasidone. With the exception of a significantly lower all cause treatment discontinuation rate with olanzapine, TGAs had no efficacy advantages over perphenazine in any of the papers publishing the CATIE results so far. Despite monthly monitoring, a remarkable 74% of patients (1061 of the 1432 who received at least one dose) discontinued their antipsychotic medication over an 18-month period: 64% of those assigned to olanzapine, 74% assigned to risperidone, 75% of those perphenazine, 79% assigned to ziprasidone, and 82 % of those assigned to quetiapine (Lieberman et al. 2005). The majority of patients in each group discontinued their assigned treatment due to inefficacy or intolerable side effects or for other reasons (Lieberman et al.2005).

The CUtLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study) study, sponsored by the UK National Health Services (NHS), refuted hypothesis that the use of TGAs amisulpride (n=13), olanzapine (n=50), quetiapine (n=23) and risperidone (n=22) is superior to the use of FGAs (chlorpromazine n=8, droperidol n=1, flupentixol n=1, flupentixol decanoate n=2, fluphenazine decanoate=3, haloperidol n=8, haloperidol decanoate n=2, loxapine n=3, pipotiazine palmitate n=2, trifluoperazine hydrochloride n=21, zuclopentixol n=5, zuclopentixol decanoate n=3) and SGAs (sulpiride n=58, thioridazine n=1) in terms of quality of life (Jones et al. 2006). Beside the primary outcome criterion quality of life, other outcome measures like symptoms, adverse effects, patient satisfaction and costs of care showed no advantage of TGAs over FGAs. In the treatment resistant arm of the CUtLASS study, the SGA clozapine was found to be advantageous over the TGAs, while there was no advantage of the TGAs (46% had been treated with olanzapine) compared to the group of older antipsychotics in which 49% of patients had received the SGA sulpiride, very similar to TGAs amisulpride (see Lewis et al. 2007, Jones et al. 2006, Fleischhacker & Goodwin 2009).

The CAFE (Comparison of Atypicals in First Episode of psychosis) study showed that all cause treatment discontinuation rates were high in all three (risperidone, olanzapine and quetiapine) groups, but did not statistically differ from one another (McEvoy et al. 2007). Also, no difference was found for changes in scores on the PANSS (Positive and Negative Symptoms Scale).

The EUFEST (European First Episode Study in Schizophrenia) study, funded by the European Group for Research in Schizophrenia with grants from Astra Zeneca, Pfizer and Sanofi Aventis, showed that in patients with first-episode schizophrenia and schizophreniform disorder, treatment discontinuation rate over 12 months was significantly higher in patients treated with a low dose of the FGA haloperidol (n=103) than in those treated with the TGAs (amisulpride n=104, olanzapine n=105, quetiapine n=104 or ziprasidone n=82), with the lowest discontinuation in

olanzapine group (Kahn et al. 2008, Fleischhacker et al. 2005).

The effectiveness study by McCue et al (2006), not supported by pharmaceutical industry, measured improvement in mental status so that the patient no longer required acute in-patient care and showed that olanzapine (92%), haloperidol (89%), and risperidone (88%) were significantly more effective than quetiapine (64%), ziprasidone (64%) and aripiprazole (64%).

The 12-month randomized, double-blind effectiveness study by Rosenheck et al (2003), sponsored by Veterans Administration measured care costs and side-effects of olanzapine vs. haloperidol treatment in 309 patients with schizophrenia and schizoaffective disorder and found no difference between treatment groups in study retention; positive, negative or total symptoms of schizophrenia; quality of life; or extrapyramidal symptoms (see also Moeller 2008).

Generally speaking, the results of PCTs are very pessimistic: 1. TGAs have no significant advantages over older generations of antipsychotic medications; 2. there is no significant differences in efficacy and effectiveness between antisychotic drugs; 3. treatment non-adherence and discontinuation rates are very high among patients treated with all antipsychotic drugs. An important epistemiological concern is related to remarkably high discontinuation rates in PCTs what indicates a low treatment acceptability by the patients. Treatment non-adherence and discontinuation may be associated not only with lack of insight, and current and past adverse events but also with relapses, the patient's perspective of disease and treatment in general, involving confidence in psychopharmacotherapy, the quality of doctor-patient relationship involving mutual trust, patient's subjective satisfaction with treatment and current medication regimen as well as beliefs about treatment, illness and mental state.

DEMYTHOLOGIZING „CONTROLLED CLINICAL TRIALS“: MISUNDERSTANDING, FRAUD AND SPIN

The distinction between real or true and artifact or false results and its interpretation is not an easy task. Clinical trials are based on different philosophies of treatment, so that psychopharmacological data raises a range of epistemiological, conceptual and ethical questions. Various answers to these questions are related to applied mechanistic, formistic, contextual or systemic thinking or information-processing meta-strategies (Jakovljević 2008).

We have been continuosly faced with the problem of evaluating the results of RCTs as well as those of PCTs, and their translating into every-day clinical practice concerning relative efficacy and effectiveness of antipsychotic medications. Although there is no doubt that RCTs and PCTs are our best available methods for evaluating the efficacy and effectiveness of an antipsychotic treatment, there are three striking problems common in clinical psychiatric trials: misunderstanding, fraud and spin (see Marshall 2004).

„Misunderstanding“ is related to what a treatment is and how treatment concepts were changed over time (Marshall 2004). A good example of misunderstanding of data from clinical trials is the comparison of effectiveness of the so called typical and atypical antipsychotics and rigid explanations of the inconsistent study results.

Conceptual misunderstandings clarification is related to the distinction of genuinely scientific theories from pseudoscientific theories, proper classification of antipsychotic drugs, design of clinical trials and treatment outcome criteria definitions, generalizations of results from one antipsychotic to the other antipsychotics classified in the same group. On the basis of our former ignorance, all antipsychotic drugs were classified pseudoscientificaly in two groups: typical (conventional or classical) and atypical or modern antipsychotics (see Table 1) what is useless and misleading. This distinction has outlived its usefulness. Also, the generalization of findings with perphenazine to other FGAs from 1950s and 1960s like haloperidol and fluphenazine, may be misleading, prejudiced and prejudicial.

Since 1990s, a number of new antipsychotic agents have appeared, providing new treatment options and increasing optimism for better clinical recovery and treatment outcome. All these TGAs (risperidone, olanzapine, sertindole, quetiapine, ziprasidone, aripiprazole, amisulpride) with the second generation antipsychotics (SGAs) from 1970s and 1980s (e.g. clozapine and sulpiride) are commonly lumped together as the class of atypicals, despite the great differences among these antipsychotics in their clinical and pharmacological profiles. Despite the possessing different effects on different specific syndromes, they are

Table 1. Pseudoscientific «typical vs. atypical antipychotics» classification and 5-HT2A/D2 receptors affinity ratio (according Shiloh et al. 1999)

Class	Generic name	5-HT2A/D2	D2/5-HT2A
So called typical antipsychotics			
phenotiazines	chlorpromazine	10:1	
	fluphenazine		2:1
	levomepromazine	5:1	
	perphenazine	2:1	
	thioridazine	5:1	
	trifluoperazine	2:1	
thioxanthenes	chlorprotixene	30:1	
	thiothixene		40:1
	zuclopenthixol		3:1
miscelaneous	clothiapine	15:1	
	haloperidol		25:1
	loxapine	7:1	
	molindone		8:1
	pimozide		5:1
So called atypical antipsychotics			
	clozapine	30:1	
	olanzapine	50:1	
	quetiapine	1:1	
	risperidone	8:1	
	sertindole	100:1	
	sulpiride		50:1
	ziprasidone	3:1	

classified misleadingly as very similar, almost identical in the same group from a given subjective point of view. Syndrome specificity effects are related to the specific treatment response that may significantly improve global treatment response.

Fraud is defined as deliberate falsifications of study results (Marshall 2004). „It is hard to be certain that fraud has occurred unless someone confesses to it, but it is not unusual in the course of a systematic review to come across anomalies that raise questions about the veracity of the data“ (Marshall 2004). Spin is defined as an attempt to mislead that falls short of actual falsification (Marshall 2004). According to Marshall (2004) three common types of 'spin' can be identified: 1. spinning by selective reporting (e.g. not reporting a disappointingly negative finding), 2. spinning using rating scales (e.g. evaluating outcome using multiple rating scales, or unpublished scales), 3. meta-spinning (e.g. reviewer's pessimistic or optimistic looking on inconsistent results of clinical trials). Fraud in pharmacological trials of schizophrenia is probably rare, whereas 'spin' is endemic.

EVIDENCE-BASED PRACTICE AND PRACTICE-BASED EVIDENCE:

Do clinical trials show us the «real world» (truth)?

Inconsistent and controversial results of RCTs and PCTs is a multi-interpretable phenomenon and can be explained from different theoretical and conceptual perspectives. Each perspective has a different internal logic, specific and distinct information processing strategy and plausible interpretation as well as different practical implications.

All clinical psychiatrists have seen some patients respond to an antipsychotic medication and not to another, not only from different class, but also from the same class. It is a truism that individual patients respond differently to different antipsychotics. With application of evidence-based medicine (EBM), clinical psychiatrists also apply their own experience, knowledge and intuition. According to the Institute of Medicine (2001) evidence-based practice should be an integration of the best research evidence with clinical expertise

and patient values (Azrin & Goldman 2005). „Best-based practice refers to clinically relevant research, often from the basic health and medical sciences, but especially from patient-centered clinical research into the accuracy and precision of diagnostic tests, including the clinical examination; the power of prognostic markers; and the efficacy and safety of therapeutic, rehabilitative, and preventive regimens. Clinical expertise means the ability to use clinical skills and past experience to rapidly identify each patient's unique health state and diagnosis, individual risks and benefits of potential interventions, and personal values and expectations. Patient values refers to the unique preferences, concerns, and expectations that each patient brings to a clinical encounter and that must be integrated into clinical decisions if they are to serve the patient“.

Regarding the purpose of clinical trials, the four different ethical paradigms have emerged from the perspective of the competing ethics in professional life: 1. Caring ethic (primacy given to caring for others with protecting the rights of the patients), 2. Service ethic (primacy given to contractual relationship in service with recognition of reciprocal rights and duties), 3. Public office ethic (primacy given to the service of the common good related to social justice and equity), and 4. Bussines ethic (primacy given to serving customer (sponsor) needs and customer (sponsor) satisfaction (see Thompson 1995). RCTs includes many aspects of the bussines ethic, while public office ethic is more involved in PCTs. RCTs, usually sponsored by pharmaceutical companies, are often accused of being heavily biased or marketing-based in favor of sponsor's antipsychotic drug, even phase III studies used to license a drug. It is important to note that all RCTs used for licensing a drug are under strict methodological control by drug authorities (FDA, EMEA). PCTs, sponsored by government institutions or insurance companies, may be influenced by their aim to prove beneficial aspects of a cheap, older antipsychotic drug (Moeller 2008). The CATIE and the CUtLASS studies have been used to argue for restricting coverage for costly TGAs, but the actual advantage of these “effectiveness” studies on antipsychotics remains questionable (Moeller 2009). So, public policy regarding the role and place of modern antipsychotics in schizophrenia treatment seems to be guided by the imperfect state of clinical trials and by economic constraints (Rosenheck 2005). A major weakness of the current methodology and regulatory standards is that they give little space for profiling antipsychotic drugs because heterogenous patients samples are studied, and outcome measures are used to allow little differentiation of therapeutic effects on distinctive syndromes (see Sigfried 2001). Without profiling antipsychotic drugs and investigating differences between them, their specific profiles, advantages and disadvantages, we ignore in clinical trials a fundamental true that there is no such thing as an antipsychotic equally beneficial, efficacious, safe and acceptable for all patients with same diagnosis.

CREATIVE ANTIPSYCHOTIC PSYCHOPHARMACOTHERAPY AND PERSONALIZED MEDICINE

Although large clinical trials did not find any antipsychotic medication to be clearly superior it is not true that antipsychotics used in equivalent doses are equal for every patients with schizophrenia. Small, statistically insignificant but clinically important differences between antipsychotics may be easily missed in both RCTs and PCTs. Routine practice-based evidence indicates that all antipsychotic drugs differ in their efficacy, tolerability, acceptability and safety. FGAs, SGAs and TGAs are not homogenous groups as well as wrongly called typicals and atypicals. All, FGAs, SGAs and TGAs classes are very broad and include some distinctly different antipsychotic medications. From pharmacological point of view we can differ four classes of so called atypical antipsychotic: selective dopamine antagonists (sulpiride, amisulpride), dopamine stabilizers (aripiprazole), serotonine-dopamine antagonists - SDA (risperidone) and multiple antagonized receptors targeted antipsychotics – MARTA (clozapine, olanzapine, quetiapine).

Psychiatry, as well as clinical psychopharmacology is in the process of a paradigm shift (see Jakovljević 2009, 2008, 2007a). Instead of relatively broad pathological diagnoses, population-based risk assessments, and nonspecific “one-size-fits-all“ therapies, we are moving to an individualized and personalized medicine. The concept of personalized medicine is based on hypothesis that each patient is unique human being with unique genotype and phenotype, personal and family history, life story and script, one or more

comorbid diseases, specific nutritional habits and specific preferences in medication taking not always in concordance with recommended ones. Personalized medicine offers highly specific and individually adjusted treatment for a concrete patient in a given circumstances. Personalized psychopharmacotherapy pursues trends in personalized medicine. In addition to the influence of genetic, personal and environmental elements, it encompasses also influence of comorbidity on pharmacodynamics and pharmacokinetics of antipsychotic medications as well as on possible drug interactions.

Following this concept, patients with schizophrenia should be treated as individuals and not as members of a diagnostic group F20-F29 on whom a uniform treatment according to official guidelines is performed (see Jakovljević 2007b). Each patient with schizophrenia being considered for antipsychotic medication should be evaluated according to her or his own unique model with the goal of optimal treatment outcome. In other words different patients with schizophrenia should receive different treatments according to different perspective truths. The practice of mental health care should not be only a scientific exercise but also an exercise in humanity, informed by ethical and moral choices (Laugharne 2004). The choice of antipsychotics should be determined on an individual basis, taking into account patient preference, sensitivity, comorbid conditions, specific pharmacological profile of antipsychotic medications, the relative and specific efficacy of each medication. Given the fact of double-sided aspects of antipsychotic drugs, scientific, rational, creative and successful psychopharmacotherapy of schizophrenias is a matter of estimating risks (possible adverse effects) and benefits (therapeutic effects) ratio on the basis of functional psychopathology and person-centered psychiatry.

Personalized medicine approach in psychiatry has started to change theory and practice of clinical trials searching for better mental health care for patients with schizophrenia based on proper evidence.

CONCLUSION

Third generation antipsychotics were developed with the promise of enhanced efficacy, improved safety and tolerability, and better acceptability relative to their first and second generation predecessors. However, pragmatic clinical trials like CATIE and CUtLASS sponsored by government authorities have challenged the current worldview of the greater advantages of third generation over first generation antipsychotics and suggested more clinical applicability of older antipsychotics. Clinical thinking and making treatment decisions should be based primarily on systematic, rational and creative thinking, not on statistic, reductionistic, formistic and mechanistic ones dominant in clinical studies. Development of personalized psychopharmacotherapy of schizophrenia depends on the availabilty of enough number of modern antipsychotics to be the first choice treatment for this devastating mental disease. The goal for the next decade in clinical psychopharmacology of antipsychotics will be to use the current medications more rationally, to match patients to antipsychotic drugs individually in the spirit of creative psychopharmacotherapy and personalized medicine, and to continue the search for mental health drugs of more effectiveness.

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