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The Comparative Efficacy of Therapy with Typical and Atypical Antipsychotics

Kasimov A. A., Abdullayeva N. N, Begbo'tayeva S. B., Nizamov X. M.
Department of Neurological Diseases Samarkand State Medical University

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ABSTRACT

In 2021, the authors published a literature review highlighting the comparative efficacy of typical and atypical antipsychotics. The review reflected the progress of a review of the differences between first- and second-generation antipsychotics. It was initiated by the publication of a series of studies using meta-analysis. Since the publication of that review, the issue has been widely reported in the Western literature on the basis of new studies on the issue and the debate surrounding them, making a further synthesis of relevant new data necessary.

Introduction. Among the studies underlying the growing controversy about the properties of antipsychotic medication, work carried out in settings close to actual clinical practice stands out. Cut Lass

The CATIE study is one of the first major studies on the effectiveness of therapy for schizophrenia. The first phase compared the effectiveness of four atypical antipsychotics (olanzapine, quetiapine, risperidone and ziprasidone) and the typical antipsychotic perphenazine. A total of 1493 patients aged 18-65 years from 57 centers in the USA were included in the study. Excluded from the study were patients with schizoaffective disorder, mental retardation or other cognitive impairment, a history of adverse reactions to drug therapy, who had only one schizophrenic episode prior to the study, with a history of treatment resistance (persistence of severe symptoms despite adequate treatment attempts). One of the drugs used in study or treatment with clozapine), pregnant women and breastfeeding, as well as patients with an unstable somatic condition. Of particular note are the broad inclusion criteria in this study, which relate its conditions to actual clinical practice. Olanzapine was used in doses ranging from 7.5 to 30 mg/day, perphenazine from 8 to 32 mg/day, quetiapine from 200 to 800 mg/day, risperidone from 1.5 to 6 mg/day, and ziprasidone from 40 to 160 mg/day. Patients were treated for 18 months. Overall, 74% (1061 out of 1432) discontinued treatment before the end of the

study: 64% were on olanzapine, 75% on perphenazine, 82% on quetiapine, 74% on risperidone, and 79% on ziprasidone. Within limited efficacy in the olanzapine group treatment interruption was less common than in other groups, suggesting that olanzapine is more effective other drugs. The use of olanzapine was not different from that of other modern antipsychotics. No differences were observed between the other modern antipsychotics and perphenazine. It is important to note that the differences between perphenazine and olanzapine were small. And with olanzapine, greater changes in body weight, glucose and lipid metabolism were observed than with the other drugs. In addition, treatment with olanzapine was interrupted more frequently than with the other study drugs due to intolerable side-effects.

The results of the first phase of CATIE have been supplemented by a number of publications. For example, R. Keefe et al., based on the fact that the study included patients with neurocognitive impairment, noted some improvement in relevant indices as a result of therapy without differences in the effect of different drugs on them. No differences were found in changes in quality-of-life indicators in different patient groups , and it was also noted that perphenazine was the most cost-effective, as it was no less effective than other drugs at a lower cost. An analysis of the psychosocial functioning of patients was also published, which showed an improvement after 18 months of therapy, but no differences were found between the treatments. Critics of the CATIE study pointed to the frequency of treatment switching in this study, including the fact that only 40% of patients took drugs at the maximum dose, although their intolerance was the reason for treatment switching in only 15% of cases. However, most other authors note that some methodological errors do not invalidate the results of this study.

The CutLass study was funded by the UK government. Its particular feature was to compare typical and atypical antipsychotics as separate classes of drugs, within which the treating physician was free to choose one or the other. A total of 1,227 patients with schizophrenia receiving first- and second-generation drugs; whose previous therapy had been changed due to poor tolerance or insufficient efficacy were included in the study. Patients were randomized into two groups. The mean age of the patients was 41±11 years and the mean duration of disease was 19±11 years. 80% of patients were on first-generation medication prior to study inclusion. The severity of psycho-pathological symptoms at the time of study inclusion was mild: an overall PANSS score of 73±17 (in this regard, the study was similar to the CATIE, with a mean of 76±18). Among first-generation medications, 58 patients received sulpiride (eglonil) at an average daily dose of 813 mg, 21 received trifluoperazine (triftazine) at an average daily dose of 12 mg, and 8 received haloperidol at an average daily dose of 22 mg. In group of patients receiving second-generation drugs, 13 were prescribed amisulpiride in the average daily dose of 610 mg, 50 - olanzapine in the average daily dose 15 mg, 23 - quetiapine at an average daily dose of 450 mg and 22 - risperidone at an average daily dose of 5 mg. Replacement therapy was carried out within the same class of drugs. A year later, 85% of patients from the group receiving first-generation drugs were examined, and 78% of patients - second generation. It was noted that the improvement observed in most patients was not significant: PANSS scores decreased by an average of 8.3 points in patients treated with the first-generation drugs and by 5.1 points in patients treated with the second-generation drugs. The changes in the quality-of-life parameters were also not significant. Patients who received first-generation drugs changed from 43±22 to 53±21 points, patients of the second generation changed from 44±20 to 51±20. There were no significant differences between the groups in the manifestation of depression (according to the Calgary questionnaire) and the severity of side-effects of movement disorders. In addition, this study attempted to assess patients' attitudes towards therapy using the Drug Attitude Inventory. However, no significant differences between the groups were found in this indicator either. The QALYs (quality-adjusted life years) were significantly higher with first-generation drugs. It should be noted that most patients in this study also changed therapy due to insufficient efficacy

(in 44% of the first-generation drug subgroup and 54% of those using second generation drugs) and adverse events (30% of first-generation drugs and 12% of second-generation drugs) or both (26% of first generation and 34% of second-generation drugs). The second phase of this study compared clozapine with other second-generation drugs. The study had a similar design to the first phase. It included 128 patients in whom treatment with two or more drugs was not sufficiently effective. The effectiveness of the therapy was assessed using QALYs. The study showed a significant superiority of clozapine over other drugs.

The CutLass study has caused a wide resonance in the literature, especially with regard to its shortcomings. Thus, D. Naber and M. Lambert pointed out that the low efficacy of therapy in general and the blurring of differences between drug groups may be due to the chronic nature of the disease in the patients included in the study. Others pointed out that the typical antipsychotic in this study was sulpiride (given to nearly 50% of patients), although haloperidol is more commonly used for this purpose in most countries. Moller, R. Tandon et al. (28) noted the retrospective nature of the evaluation, which may have been influenced by the heterogeneity of the group of drugs in both classes.

Among the common shortcomings of CATIE and CutLass in the studies cited above was the chronic nature of the disease in the patients included in the studies and the possibly associated decreased sensitivity to differences between the drugs. Was it has been suggested that greater differences could be found in patients with first psychoses? Examples that support this view can be found in studies such as SOHO and EUFEST, mentioned at the beginning of the review.

The SOHO study was conducted in 10 European countries. The study enrolled 2960 patients with a mean age of 42±14 years, a disease duration of 7.6±1.7 years, and a baseline CGI of 4.4±1.0. The results of 2-year treatment with antipsychotics showed that patients treated with second- generation drugs had a greater chance of achieving remission than those treated with first-generation drugs. However, M. Lambert et al. point out that this study was not randomized. Moller criticizes the study for its performance evaluation, noting the unrepresentativeness of the samples and the presence of comorbidity in the subjects.

The EUFEST results were published in 2008. A total of 498 patients were included, with an average age of 26±6 years. In these patients, positive symptoms of schizophrenia had manifested less than 2 years previously, these patients had received antipsychotic therapy for no more than 2 weeks previously, and 33% had received no antipsychotics at all. At baseline, the overall PANSS score was 89±21. The second- generation drugs in this study were compared with low-dose haloperidol (3.0±1.2 mg/day). Most patients showed symptom reduction, and there were no significant differences in PANSS between patients receiving haloperidol and second-generation drugs. However, significant differences were found using the General Clinical Impression Scale (CGI) and the Global Assessment of Functioning. A greater improvement on these measures was observed in patients receiving amisulpiride and olanzapine. Quetiapine and haloperidol recipients showed less change. There was also a significant difference in the rate of consent to follow-up: 60% of amisulpiride users, 67% of olanzapine, 47% of quetiapine and 55% of ziprasidone users continued treatment; 28% of those receiving haloperidol continued it. Differences in the frequency of motor side-effects were also noted in this study.

In recent years, several meta-analysis studies have also been carried out with different groups of relevant papers.

In 2019, S. Leucht et al. published the first meta- analysis of 150 double-blind studies. They combined follow- up of 21,533 patients. The duration of 121 of the 150 studies was less than 12 weeks. They compared the effectiveness of first- and second-generation oral antipsychotics in treating schizophrenia (only studies using optimal doses of the new drugs were analyzed). Various typical antipsychotics were used: galoperidol in 95 studies, chlorpromazine in 28, and

other drugs in the others. Their analysis showed that amisulpiride, clozapine, olanzapine and risperidone are more effective in reducing symptoms (on a number of scales) than first-generation drugs. In addition, each of the newer drugs was found to have a different side-effect profile and a lower risk of extrapyramidal side-effects than the first- generation drugs, but these differences were less pronounced. No difference in weight gain was found between atypical antipsychotics and first-generation drugs. However, only seven studies were analyzed for this parameter. Quality of life indicators, which were examined in 17 of 150 studies, were only higher with amisulpiride, clozapine and sertindol than with typical antipsychotics. The frequency of psychiatric exacerbations was significantly reduced with risperidone, sertindol and olanzapine compared to first-generation drugs (although only 14 were involved). The authors of this meta-analysis note that the differences in efficacy between the drugs are not significant for the choice of therapy and differences in the frequency and nature of side-effects are more important, i.e., the new drugs are not, in their opinion, "revolutionary".

The second publication by S. Leucht et al. using a meta-analysis was also published in 2019. It compared second-generation drugs against each other on a PANSS scale. The study showed superiority of olanzapine over aripiprazole, quetiapine and risperidone and superiority of risperidone over quetiapine and ziprasidone. A more detailed analysis of the PANSS scale showed that the differences observed were mainly related to changes in positive symptoms. However, the mean differences between olanzapine and risperidone were small and slightly larger when comparing olanzapine and ziprasidone. The authors of this paper concluded that, for clinical practice, "Small benefits in efficacy must be weighed against large differences in side-effect profile and cost". Also important is the opinion of the authors in this publication that dividing antipsychotics into typical and atypical leads to some terminological confusion. They therefore proposed a change in the characterization of second-generation drugs: "Second-generation drugs differ in many ways, including efficacy, side-effects, price (some are now 'generics') and pharmacological features (amisulpiride is not a serotonin receptor blocker). They are, like the first-generation drugs, not a homogeneous class.

Other researchers also agree with the above view. For example, P. Tyrer and T. Kendall write that the definition of "second-generation antipsychotics" as atypical is indeed inaccurate, as second-generation drugs have no particular atypical properties that would distinguish them from typical first-generation antipsychotics. These authors point out that “on the evidence currently available from various sources, it is not difficult to assume that second-generation antipsychotic studies were conducted more for marketing reasons than for clarifying the truth of the situation for clinicians and patients".

D.Naber and M. Lambert, reflecting on the systematics of antipsychotics, analyses the evolution of the terminology. They point out that the very name "atypical" was associated with the supposed absence of motor side- effects. However, when these drugs were also found to cause extrapyramidal disorders in high doses, the concept of atypicality became quantitative rather than categorical. According to these authors, recent studies show that this principle of separation is also pseudo categorical.

Conclusions:Thus, summarizing the studies conducted in the last 5 years, there is a lack of evidence in favor of tangible advantages of one class of drugs (second generation, atypical) over another (first generation, typical). There is a growing consensus that the classification of antipsychotics into classes is inappropriate. The choice of therapy should be based on the characteristics of individual drugs rather than on the characteristics of the respective class, the existence of which is increasingly questionable.

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