

## Editorial Άρθρο Σύνταξης

# Comparison of first and second generation antipsychotics: An update

The modern era in the treatment of psychotic disorders began in the early '50s with the discovery of chlorpromazine. This was a real revolution and maybe the most important single contribution in the treatment of psychiatric illnesses. Chlorpromazine and the subsequent drugs that were introduced in the next 10–15 years, shared a common element in that they all were potent dopamine-2(D<sub>2</sub>) receptor antagonists.

The next landmark in the pharmacotherapy of psychoses was the introduction, in the early '90s, of the novel or atypical or second generation antipsychotics (SGAs). The prototype of these new drugs was clozapine, an "old" drug, originally synthesized in 1958. What all new agents have in common –in contrast to the traditional antipsychotics- is similar or greater activity at serotonin receptors than at dopamine type 2 receptors and for this reason they have been called serotonin-dopamine antagonists.

In the ensuing years due to the accumulated experience in the use of SGAs, a widespread belief has been developed that the new agents are superior to neuroleptics as: (1) they have similar, if not better, efficacy on the positive symptoms, (2) they have advantages in terms of improving negative symptoms, (3) they ameliorate cognitive function either directly or as a secondary effect of avoiding side effects, (4) there is some evidence that they improve depressive symptoms, (5) they have fewer side effects, especially extrapyramidal symptoms, (6) there is better compliance and greater subjective acceptance by the patients.<sup>1</sup> Therefore, SGAs are considered as first-line treatment in schizophrenia and other psychotic disorders. However, two large meta-analyses reach conflicting conclusions. In the first one, Geddes et al<sup>2</sup> made a systematic overview and meta-regression analysis of 52 randomized controlled trials comparing SGAs and first generation antipsychotics (FGAs). They concluded, that when the dose was  $\leq 12$  mg/day of haloperidol or equivalent, SGAs have no benefits in terms of efficacy. In addition, they stated that SGAs cause fewer extrapyramidal side effects, but overall tolerability is similar to FGAs, as this advantage is counterbalanced by the presence of other side effects. In contrast, Davis et al,<sup>3</sup> in a more recent and larger meta-analysis of 124 randomized controlled trials, reported that some of the SGAs such as clozapine, olanzapine, risperidone and amisulpride are more efficacious than FGAs while other such as ziprasidone, quetiapine, aripiprazole and sertindole seem to have the same efficacy as the "older" drugs. Furthermore, they supported that they did not find any significant effect of haloperidol dose, ( $\leq 12$  mg/day/ $>12$  mg/day) or equivalent and concluded that SGAs are not a homogenous group, as far as their efficacy is concerned. Regarding tolerability, the researchers criticize the conclusions of Geddes et al,<sup>2</sup> overemphasize the manifestation of fewer extrapyramidal symptoms by SGAs and underscore their overall tolerability. Their final conclusion, is that SGAs, or at least some of them, are first line drugs.

During the last 3 years, 3 large studies have been published. These studies differed from the previous as their design and methodology were closer to "real world", closer to everyday clinical practice. In the first one, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)<sup>4</sup> which was sponsored by the National Institute of Mental Health, 1460 schizophrenic patients were randomly assigned to receive olanzapine, quetiapine, risperidone, ziprasidone or perphenazine for up to 18 months. The results of the study were far from encouraging as 74% of the patients discontinued their medication for any cause before 18 months. Olanzapine performed better (64%) and quetiapine worse (82%). The time to discontinuation of treatment was significantly longer in the olanzapine group compared to the quetiapine and risperidone groups, but not in comparison to the perphenazine group. The time to discontinuation of treatment for lack of efficacy was longer for olanzapine than for quetiapine, risperidone and perphenazine. However, regarding total PANSS scores, although the greatest improvement initially appeared in the olanzapine group, its advantage diminished over time. There were no significant differences between groups in time until discontinuation owing to side effects. However, olanzapine was associated with more discontinuation for weight gain and metabolic effects and perphenazine with more discontinuation for extrapyramidal symptoms. In general, the various drugs studied were similar, with olanzapine being relatively more effective, as measured by treatment discontinuation. This might be due to the more optimal dose of olanzapine compared to the other agents, a fact for which the study has been criticized.

The second study, the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS1),<sup>5</sup> which was funded by the NHS in the United Kingdom, compared FGAs and SGAs (other than clozapine), as classes, across 1 year. There were no significant differences between groups on quality of life (which was the primary outcome measure), on the PANSS scores, on the Calgary Depression Scale for Schizophrenia score, on the GAF score and on scores of scales measuring acute extrapyramidal symptoms. In fact,

FGAs were associated with a slightly greater improvement in quality of life and in PANSS total score, but differences, as mentioned, were not statistically significant. The study has been criticized for some methodological approaches, such as the selection of the individual drug in each class by the responsible consultant psychiatrist, the quality of life was the primary outcome measure, sulpiride – a not very “popular” drug – was the most commonly chosen FGAs, etc. Despite all the above, the results of the study are remarkable.

The third and more recent study is the European First Episode Schizophrenia Trial (EUFEST),<sup>6</sup> a multicenter study in 14 different countries. According to the study design, 498 practically first-episode psychotic patients, were randomly assigned to 4 SGAs (olanzapine, quetiapine, amisulpride, zipradisone) or to haloperidol. The results of the study showed that, treatment discontinuation for any cause was significantly higher in patients taking haloperidol than in those taking any SGA. In addition, treatment discontinuation of insufficient efficacy was, similarly, higher in patient on haloperidol than in those on SGAs, although the difference between haloperidol and quetiapine was not significant. The olanzapine and amisulpride group had the lower rates of discontinuation due to the lack of efficacy. Global improvement, as measured by the CGI and GAF scales, differed between treatments with most improvement recorded with amisulpride and least with haloperidol and quetiapine. However, the reduction of PANSS scores, the rates of admission to hospital and the adherence to antipsychotic drugs did not differ significantly between groups. Treatment discontinuation rates because of side effects differed between treatments, mainly due to the better tolerability of quetiapine and olanzapine compared to haloperidol. The researchers conclude stating that they cannot support that SGAs are more efficacious than is haloperidol.

Regarding compliance, in addition to the finding of the previous study, a recent review<sup>7</sup> reports that compliance behavior of the patients has only marginally improved since the introduction of SGAs.

From all the above, it clearly seems that the great initial enthusiasm regarding the superiority of SGAs versus the FGAs has considerably been diminished and today, the appraisal of the comparison between the two classes is more realistically based. This enthusiasm was justified, as it has been encouraged, at least partly, by an overly expectant community of psychiatrists and patients and their families eager to believe that much “better” drugs, in all the aspects, now exist. The more realistic approach today is reflected on the last revision of guidelines of Texas Medication Algorithm Project (TMAP).<sup>8</sup> There, the first recommendation is again, as in the previous TMAP version of 2003, that SGAs are preferred for treatment of first episode of schizophrenia, but this time it has been established by majority opinion, unlike by group consensus in 2003. Furthermore, the second recommendation states that FGAs are an option in stage 2 of the antipsychotic algorithm after a trial of 1 SGA. In the previous version it was recommended that monotherapy with FGAs is an option in stage 2A, after trials of 2 SGAs (other than clozapine), while in the older version of 1999 FGAs were recommended as an option in stage 4 after trials of 3 of the SGAs.

All the above comments do not have the intention to downgrade the important contribution of the SGAs in the pharmacotherapy of schizophrenia and other psychotic disorders, but to underscore the urgent need for greater progress in developing novel therapeutic intervention. This effort seem that has already started. For instance, a recent phase II clinical trial supports the antipsychotic efficacy of an mGluR 2/3 receptor agonist.<sup>9</sup> If confirmed in future studies, this could be the first antipsychotic without direct action on dopamine receptors.

In conclusion, the discovery of chlorpromazine was a real revolution. The introduction of SGAs was an important step forward but not a revolution. Now, the time has probably come for the development of third generation antipsychotics agents with different pharmacological profile, more efficacious and more “friendly” regarding side effects.

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