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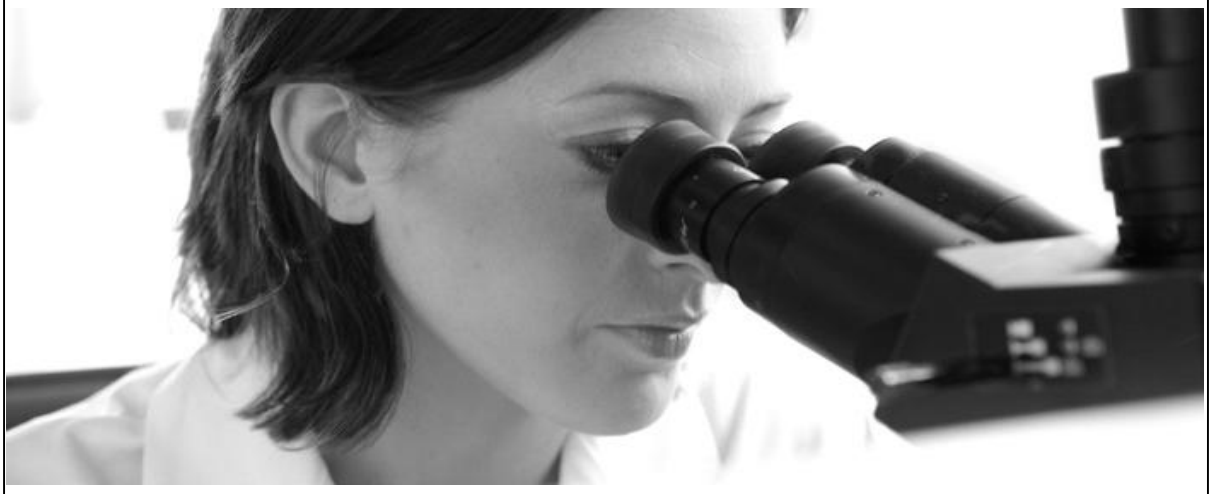

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RESEARCH ARTICLE

PROGRESS IN THE LONG TERM TREATMENT OF SCHIZOPHRENIA (THE GIANT LEAP OF OLANZAPINE DEPOT ERA)

Stoynov K., Ganev I* and Donchev T

Clinic of Psychiatry, Military Medical Academy-Sofia, Sofia, Bulgaria

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ABSTRACT

The primary objective was to present our experience in the application of olanzapine injection for treatment of schizophrenia. The use of depot antipsychotics has many advantages and the low drug compliance is the main factor leading to selection of depot injections. Managing non-compliance is exceptionally important task which, though, has been solved namely due to the successful application of depot antipsychotics. The first line of therapy is occupied by atypical antipsychotics such as olanzapine. The efficacy of treatment with olanzapine depot has been clinically evaluated by measuring CGI at each application for each patient. Three-hour supervision by staff has been provided as well as a standard operating procedure for involving resuscitation team and emergency room admission, if necessary. Three-year follow-up of CGI assessment reported a steady trend of improvement in the patients' status. Two cases of post-injection syndrome have been registered and managed promptly. Despite the undeniable advantages of depot antipsychotics, in particular - olanzapine, there was a small remaining proportion of schizophrenic patients receiving such treatment. With regard to the post-injection syndrome, it turned out that it has been carried out as Bonhoeffer's exogenous type of reaction, and as such, it has effectively been treated with haloperidol.

INTRODUCTION

The advantages of depot antipsychotics are undeniable in the treatment of schizophrenia which is also entirely true in the case of first episode (Kirson *et al*, 2013).

Of course, one of the main factors that would lead the physician to the selection of a depot form is the low level of compliance which is rather a rule in schizophrenic patients especially with regard to cases of debut.

Adherence to medication in schizophrenia

The non-adherence to treatment in schizophrenic patients sums up to 41.2% (Tesfay *et al*, 2013). Many factors have been associated with the treatment non-compliance. The main ones which increase the likelihood of non-cooperation are lack of insight, negative attitude toward medication, previous non-compliance, psychoactive substance abuse, shorter course of the disease, inadequate planning of hospital discharge or extramural care, poor therapeutic relationship. In fact, the frequency of non-adherence to treatment of schizophrenia did not differ significantly from that seen in other chronic diseases (Fenton *et al*, 1997). The studied topic presents cases of discontinuation of antipsychotic therapy in the first year of its implementation by comparing treatment with depot neuroleptic and administration of oral antipsychotic. Preponderance of patients remaining on depot form compared to oral form is significant in the first year of treatment (Zhu *et al*, 2008).

The depot therapy reduces the risk of discontinuation with 59% and the risk of re-hospitalization by 64% compared to oral administration of antipsychotic. However, only about 8% receive depot therapy as a first prescription after discharge and only about 10% of the time in a total of 5221 patient-years were on such treatment (Jari *et al*, 2011).

Regarding the cases of relapse the data suggest that 42% of patients on oral and 27% of those on depot antipsychotic relapse in 1 year of duration (Gaebel *et al*, 2010). A meta-analysis showed that patients receiving depot antipsychotic have significantly greater overall improvement than the patients on an appropriate oral antipsychotic (Adams *et al*, 2001). In addition, depot therapy was not associated with a higher risk of developing late dystonias (Glazer and Kane, 1992).

Convenience and advantage of depot medications in psychiatric practice reasonably require finding and using them, as, no doubt, preferably atypical neuroleptics, such as olanzapine. More and more data accumulates about the benefits of the

*Corresponding author: **Ganev I**
Clinic of psychiatry, Military Medical Academy-Sofia, Sofia, Bulgaria

depot olanzapine in patients with schizophrenia (Kantrowitz and Leslie, 2008).

MATHERIALS AND METHODS

The patient service center for olanzapine depot was founded in 2010 in the Psychiatric Clinic of MMA-Sofia being the only one in the capital of Bulgaria. Olanzapine depot has been applied to patients treated by outpatient psychiatrists practicing in the capital and part of the psychiatric hospitals. There is a certified team that makes contact with outpatients, as the applications are carried out by a specially trained staff, also an application form reflects the patient information for contact between the sending and receiving physicians. Patient datacard has also been completed with the manipulation date, dosage details and doctor name who performed the manipulation. The center provides 3 hours of observation by a doctor and a nurse, as well as a standard operating procedure for involving resuscitation team and emergency room admission if necessary. Also provided are two separated rooms: manipulation and observational rooms, as it is not without significance to improve contact between patients and their relatives (conversations, games, movies and music) and psychoeducation to recognize the first symptoms of relapse.

The first application has been performed in the center on 24-Mar-2010. More than 2,800 applications to 146 patients have been performed in the 3-year period. The proportion of patients continuing the treatment with depot olanzapine versus those discontinuing the treatment is presented on Figure 1.

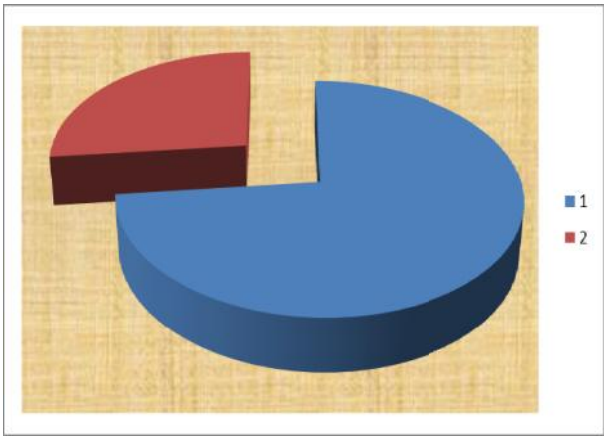

Figure 1 Patients continuing treatment with depot olanzapine versus those stopping treatment with depot olanzapine.

The blue color (1) depicts the proportion of patients who continued the treatment - 73.3%, and red (2) - discontinued olanzapine depot - 26.7%, which is a very good result, considering the high rate of patient non-adherence to drug in the general population. Reported values of non-adherence to therapy in schizophrenic patients vary, taking into account levels of nonadherence to 72% (Olivares *et al*, 2013).

The efficacy of neuroleptic depot therapy was evaluated selectively by CGI at each application, for each patient in the general population of olanzapine depot as succession is counted only in the applications. Graphically, the dynamics in the patients' condition, as measured by the scale CGI-S, CGI-I, is presented in Figures 2 and 3.

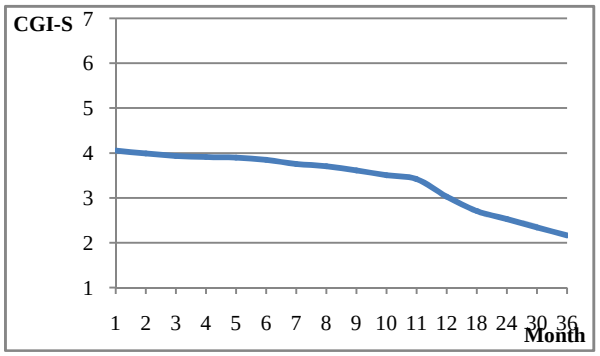

Figure 2 Dynamics in Clinical Global Impression – Severity (3-year follow-up).

RESULTS

The 3-year follow-up of the rating scale Clinical Global Impression (CGI) reported a stable trend for improvement in the condition of patients. The rate of this improvement marked a sharper decline in scores at the end of the first year. Our explanation is that this phenomenon is not exactly in relation to the drug efficacy but to the improved selection of the patients from the sending psychiatrists who include patients on depot therapy with a lower rate of psychotic scales or patients at the end of the psychotic episode. This does not compromise the quality of the achieved remission, respectively, efficacy of olanzapine depot.

The clinical experience in the Clinic of Psychiatry, MMA and the generalized treatment algorithm with olanzapine depot as well the dynamics of patient improvement measured with CGI-I are presented on Figure 3.

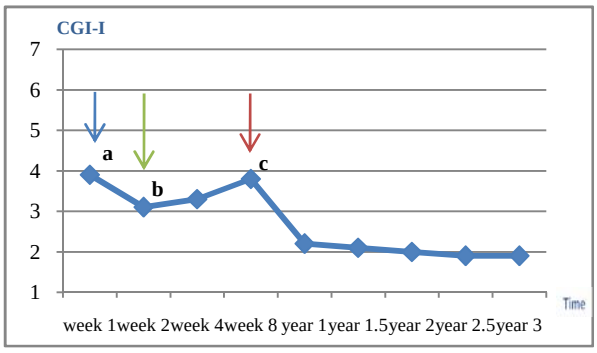

Figure 3 Generalized therapeutic algorithm and dynamics in Clinical Global Impression – Improvement.

During the first week, the treatment usually starts with an injection of zuclopenthixol acetate together with oral olanzapine, marked with blue arrow. The figure section “a-b” represents the initial patient improvement due to this first therapy. After about two weeks of treatment an application with olanzapine depot injection follows, which is marked with a green arrow in the figure. There is a deterioration of the clinical condition in part of the patients: section "b-c".

The red arrow indicates the addition of oral olanzapine to those patients, followed by a gradual improvement in CGI-I, most

clearly – at the end of the first year of treatment. The patients lacking "b-c", continue the treatment without additional oral olanzapine and the gradual improvement follows in the first year. For both groups of patients after the first year there is a stable effect of treatment with olanzapine depot seen from the values of CGI-I.

Post-injection syndrome

There have been two registered cases of post-injection syndrome after all applications managed promptly.

The following therapeutic scheme is applicable for the post-injection syndrome:

Detoxification-depuration:

- Forced diuresis with electrolytes and glucose solutions in volume corresponding to cardiovascular system and renal functions
- Non-specific antidote treatment:
- Piracetam
- Biperiden
- Vitamins B1, B6, B12
- Symptomatic treatment:
- Gastroprotective – Famotidine, Esomepromazole
- Metoclopramide
- Antihypertensive
- Antipyretics
- Sedatives –Midazolam

In case of hypotonia do not use adrenergic and dopaminergic agents!

DISCUSSION AND CONCLUSION

By extrapolating the epidemiological data there are 20000 patients in the city of Sofia suffering from schizophrenia (point prevalence), such as about 200 of them receive olanzapine depot (around 1% of patients diagnosed with schizophrenia). As demonstrated by our own experience and data from epidemiological studies, more than 40% stop medication immediately after first hospitalization, nearly 20% of first-episode psychosis patients persistently refuse medications and another 50% are non-adherent at least once within 18 months (Naber and Lambert, 2013).

The “halo effect” of the treating psychiatrist remains strictly theorized in scientific litterature with respect to the schizophrenic patient compliance to neuroleptic therapy. However it seems that this cognitive bias is also related to positive influence in patients taking long term depot treatment. The phenomenon of building good relationship “patient-doctor” leads also to improvement and due to this fact we are inclined to ignore the absence of patients with worsening on depot therapy in our offices, moreover, as biological psychiatrists we must admit our significant defense to the psychological aspects of our behavior.

The post-injection syndrome as a clinical observation does not differ from the Bonhoeffer's exogenous type of reaction described in German literature (Jaspers, 1997) but it is not a delirium and as such the psychiatric symptoms are effectively treated with haloperidol, as evidenced by the algorithm presented above.

Summary

How does the eligible patient for Olanzapine Depot look like?

- Not necessary to be mentally healthy!
- History of non-compliance or report.
- Patient’s relatives usually lack insight or are “in denial”.
- Olanzapine – oral form can be also effective.
- Female patients usually gain weight (clinical observation).

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