The effect of antipsychotic treatment in hebephrenic schizophrenia on hospitalization indicators in an adult inpatient and outpatient population

Matei Palimariciuc, Tudor Florea, Vlad Teodor Iacob,
Bianca Georgiana Secrieru, Roxana Chiriță

Matei Palimariciuc - M.D., PhD Student, assistant professor Grigore T. Popa University of Medicine and Pharmacy, Iași; junior psychiatrist, Socola Institute of Psychiatry, Iași

Tudor Florea - M.D., PhD Student, Grigore T. Popa University of Medicine and Pharmacy, Iași.

Vlad Teodor Iacob - M.D., junior psychiatrist, Socola Institute of Psychiatry, Iași

Bianca Georgiana Secrieru - M.D., junior psychiatrist, Socola Institute of Psychiatry, Iași

Roxana Chiriță - M.D., PhD, Professor of Psychiatry Grigore T Popa University of Medicine and Pharmacy, Iași, Senior psychiatrist Socola Institute of Psychiatry, Iași

ABSTRACT

Objectives: Out of all clinical forms of schizophrenia, the hebephrenic type is the least responsive to antipsychotic treatment and most difficult to manage. This characteristic results in a high average number of hospitalizations, more frequent institutionalization, generating additional cost for health care providers. With this argument in mind, we want to determine if there is a correlation between the primary hospitalization indicators and differences in antipsychotic treatment.

Methods: We anonymously collected data on all patients admitted in the Socola Institute of Psychiatry over the last five years with a confirmed diagnosis of hebephrenic schizophrenia. We logged the data regarding the age and sex of the patients, admission and discharge date, type of admission (inpatient or outpatient) as well as data regarding treatment recommendations at discharge. We performed statistical analysis, calculating for basic statistical indicators as well as variance, confidence interval, standard error and p-values.

Results: We included in our study 34 inpatients with hebephrenic schizophrenia, 19 outpatients and 4 institutionalized patients. Variance on all of the parameters we tested was

high resulting weak statistical significance. Statistically significant correlations were found between the type of antipsychotic treatment (typical, atypical, both) and hospitalization period and between the type of antipsychotic treatment (oral, depot) and duration between hospitalizations.

Conclusion: Our study found multiple correlations between the type of antipsychotic prescribed and hospitalization indicators, but due to the high variance of the samples, many of them proved not significant statistically. In the cases where a statistical significance was found, further investigation is necessary in order to establish the causal relationship between the parameters that we tested, and to establish if these correlations have a beneficial impact on the cost of the medical assistance and patients' quality of life.

KEYWORDS:

Hebephrenic schizophrenia, antipsychotic treatment, hospitalization indicators

INTRODUCTION

Schizophrenia is arguably one of the most puzzling, yet disabling of all mental disorders, with its severe and persistent psychotic manifestations accompanied by capricious cognitive deficits and profound psychosocial impairment. Although schizophrenia is discussed as if it is a single disease, it probably embodies a group of disorders with diverse etiologies, and it includes patients whose clinical presentations, treatment response, and illness trajectory vary. (1, 2, 3) According to the DSM-IV-TR nosology, the subtypes in schizophrenia include the paranoid, disorganized (hebephrenic), catatonic, undifferentiated and residual. Although they are defined by the predominant symptomatology at the time of evaluation, the schizophrenia subtypes offer a limited value in clinical and research setting (e.g., prediction of illness trajectory, treatment response). (4, 5, 6, 7, 8, 9) Hebephrenic schizophrenia, is a form of schizophrenia in which the essential features are disorganized speech, disorganized behavior, flat or inappropriate affect, and the absence of symptoms that meet the criteria for the catatonic type. Delusions or hallucinations, if present, are fragmentary and not organized into a coherent theme, unlike the paranoid type. The disorganized speech may be

accompanied by unprompted laughter, incongruous grinning and grimacing, and other oddities of behavior. The behavioral disorganization may lead to severe disruption in the ability to perform daily activities (e.g., showering, dressing, or preparing meals), which also leads to a run-down personal appearance, and their social behavior and their emotional responses that are inappropriate. A superficial and excessive preoccupation with religion, philosophy and other abstract themes may add to the listener's difficulty in following the train of thought. (2, 10, 11, 12, 13, 14, 15) On average, hebephrenic schizophrenia has the age of onset during adolescence, most commonly between the age of 15 and 25 and tends to have a rather poor prognosis due to the rapid development of "negative" symptoms, particularly inappropriate or blunted affect and loss of initiative and volition. (14, 16, 17, 18, 19) Hebephrenia should normally be diagnosed for the first time only during adolescence or as young adults. According to the ICD-10, the premorbid personality is characteristically, but not undoubtedly, rather shy and desolate. For a confident diagnosis of hebephrenia, a period of 2 to 3 months of continuous observation is usually necessary, in order to ensure that the aforementioned characteristic behaviors are sustained. (18, 19)

Hebephrenic vs Paranoid Schizophrenia

Clinical Features	Hebephrenic	Paranoid
Age of onset before age 25 yo	Likely	Less likely
Marriage	Less	More
Employment	Less	More
Family history of schizophrenia	++	+/-
Disorganized thought: tangential, illogical, incoherent or irrelevant speech, loose associations, blocking, or other formal thought disorders	++	+/-
Affect changes: Inappropriate affect, giggling, self-absorbed smiling, mood inconsistent with expressed ideas; flat affect, frozen, expressionless, impenetrable face	++ ++	+/- +/-
Behavior symptoms: Bizarre behavior, unusual, unpredictable, inappropriate, irresponsible, purposeless or withdrawn behavior not in keeping with sociocultural norms; Motor symptoms, hebephrenic traits-habitual mannerisms of an ordinary character, usually involving a single part of the body, eg, grimaces, tics, moving lips soundlessly, fidgeting with fingers, hand writing, thigh rubbing, etc; Catatonic traits- physical activity of an extraordinary and abnormal character, usually involving the whole body, eg, posturing, stereotyping, waxy flexibility, negativism, stupor, hyperkinesia, etc	++ ++ +	+/- +/- -
Delusions or hallucinations, persecution, control, passivity, symbolism (primary delusions), thought broadcasting, experiences or alienation, complete auditory hallucinations, delusional perceptions, or hallucinations in any sensory modality.	+/-	++

Table 1. Traits present to a marked degree or of a persistent nature (++); present to a mild degree or of a transient nature (+); absent (-). Adapted from Tsuang, M. T., & Winokur, G. (1974). (20)

Treatment: Although it is considered as the subtype with the poorest prognosis, there are as of yet very few studies on hebephrenic schizophrenia to recommend the best course of action in regards to the treatment, particularly the medication. Henceforth, the following assessments are based on already existing data from medical literature concerning antipsychotic treatment in schizophrenia, regardless of its subtype.

First- versus second-generation antipsychotics: The debate about the comparative advantages and disadvantages of first-generation, respectively second-generation antipsychotics in treating schizophrenia is still ongoing. (21) A Systematic Review and Meta-analysis have shown few differences of clinical importance for core illness symptoms. Its evidence has shown a clinically important benefit of

haloperidol over olanzapine for improving positive symptoms, but the benefit was scale-dependent. It was seen when the Scale for the Assessment of Positive Symptoms was used but not when the Positive and Negative Syndrome Scale (PANSS) was used. Furthermore, it has shown a clinically important benefit of olanzapine over haloperidol in improving negative symptoms when PANSS and the Scale for the Assessment of Negative Symptoms were used. (21,22) A different Systematic Review and Meta-analysis presented evidence that the second-generation antipsychotics are associated with a small increased risk for diabetes compared with first-generation antipsychotics in people with schizophrenia. As a side note, regardless of type of antipsychotic, screening for diabetes in all people with schizophrenia should be routine. (23) Additionally, tardive dyskinesia and extrapyramidal side effects are frequent side effects of treatment with first-generation antipsychotics, one theory explaining the cause being the neuronal cell damage from free radicals induced by antipsychotics. This hypothesis is supported by evidence of elevated levels of lipid peroxidation products and decreased vitamin E levels in dyskinetic patients. (24)

Antipsychotic combinations vs monotherapy: Antipsychotic monotherapy is recognized as the treatment of choice for patients with schizophrenia. Nonetheless, the co-prescription of more than one antipsychotic drug to an individual patient (polypharmacy) is suggested by some expert consensus guidelines as the last resort after exhausting monotherapy alternatives. More so, the empirical use of combinations of antipsychotic agents appears to be increasing with little research to support the relative efficacy, safety or cost-effectiveness of this practice. The pharmacological justifications

for antipsychotic combinations include seeking to achieve greater therapeutic potential by optimization of dopamine D₂ receptor occupancy, or activity across a wider range of receptors, on the basis that certain non-dopaminergic receptors, such as serotonergic, glutamatergic and adrenergic receptors, may be relevant to the pathogenesis of positive and negative symptoms. (25, 26, 27, 28, 29, 30) A comparative study between U.S. and E.U. estimates that in the U.S. 33% of patients receive two antipsychotics and almost 10% receive three, while in Europe, there are around 20% of patients with schizophrenia receiving combinations of antipsychotics. According to its data, when risperidone was added to clozapine, it showed a modest difference in the group of patients in terms of BPRS total symptoms. (31) Different open-label studies documented the fact that combinations involving antipsychotics resulted in some degree of symptom improvement. The combinations most commonly referred to in this limited literature were olanzapine with amisulpride or risperidone, and quetiapine with risperidone. However, on the basis of early case reports, these authors noted that combining aripiprazole with a non-clozapine second-generation antipsychotic could possibly worsen the psychosis. (32, 33, 34, 35, 36, 37, 38, 39) Moreover, the prescription of combined antipsychotics includes the risk of adherence problems associated with a more complicated regimen and an increased adverse effect burden due to drug interactions. (40, 41, 42, 43) In certain clinical situations, antipsychotic co-treatment may be superior to monotherapy, however the available evidence for the overall efficacy of combining antipsychotics is sparse, thus being unable to draw firm conclusions. (41, 44)

Oral vs depot antipsychotics: Non-adherence is a major challenge in schizophrenia

treatment. While long-acting (depot) antipsychotic medication are often recommended to address adherence problems, evidence on the comparative efficacy of depot versus oral antipsychotics is, as of yet, inconsistent. While no single intervention is universally effective, depot medication is considered one of the most important pharmacologic interventions available to address adherence problems in schizophrenia. However, the findings in the clinical literature regarding the comparative effectiveness of depot versus oral antipsychotics have been inconsistent. There is a hypothesis that states that the study design is an important factor possibly affecting estimates of comparative effectiveness of antipsychotic medications. (45, 46, 47, 48) Methodological limitations were found in most studies, leading to heterogeneity and difficulty interpreting data. The fundamental requirements for improved practice include better characterized patient groups (usually defined by treatment non-response), larger studies, longer observation times and more attention to safety/physical health concerns. (47)

MATERIALS AND METHODS

We searched the hospital's registry for patients with the diagnosis of hebephrenic schizophrenia, admitted between 1st of January 2015 and November 2019. During this period, we found that there were 53 patients with the above-mentioned diagnosis accounting for 253 admissions. Out of the 53 patients, 16 were admitted as outpatients, with 37 admissions in total, and 4 were chronic, institutionalized patients. We decided to include them separately in our analysis in order to maintain a homogenous population.

We indexed data about the age and sex of the patients, the length of admissions as well as the time span between admissions. Further, we logged the treatment recommendations received by each patient, at each discharge. Using Microsoft Excel 2016 program we calculated basic statistical indicators such as mean and standard deviation. Analytical statistical indicators like variance, p-values, confidence intervals and standard error were calculated using the T-test, ANOVA analysis, and Regression analysis provided by the Microsoft Excel's Analysis ToolPak. We generated the normal distribution curves for each parameter that we analysed using the NORM.DIST function in Excel.

RESULTS

A number of 53 patients were admitted in Socola Institute of Psychiatry during 01.01.2015 and the 01.11.2019, with an average number of admissions per patient equal to 4.77, or roughly 1 admission per year per patient. Out of the 53 patients, 17 were admitted as outpatients, 37 as inpatients and 4 were institutionalized. One of the institutionalized patients was treated as an inpatient since September 2018 and was included as for that moment in the inpatient category, and 4 patients were treated both as inpatients and as outpatients and were included in both categories. The inpatients had an average number of 1.21 admissions per year ($\sigma=1.02$, min=0.2, max=4.2) and the outpatients had an average number of 0.66 admissions per year ($\sigma=0.46$, min=0.2, max=2). These findings suggest that inpatients had poorer symptomatic control than outpatients, which on turn decided the type of admission for those patients.

Figures 1 (left). displaying the distribution of the average number of admissions per year for outpatients.

Figure 2 (right). displaying the distribution of the average number of admissions per year for inpatients.

Regarding the sex of the patients we found that males were overrepresented (70% males, 30% females) in all of the categories taken together: 100% of the institutionalized patients ($n=4$), 74% of the inpatients ($n=25$). A closer to normal distribution was found in the outpatient category: 56% males ($n=9$) and 44% females ($n=7$).

In the outpatient group, male patients had fewer admissions per patient (1.77) while females had on average 3 admissions per patient. The difference between admission times differed significantly between sexes. When taken by admission length with no consideration for how many patients accounted for those admissions, male patients had a statistically significant ($p=0.03$) longer average (5.88 days, $\sigma=7.22$) than females (2.14 days, $\sigma=1.79$) or a 274% increase. However, when calculating for the average number of admission days per patient, the results were not statistically significant ($p=0.12$), with an average for males of 4.77 days ($\sigma=4.35$) and an average of 2.75 days ($\sigma=2.18$) for females.

Figure 3. The sex distribution of patients in all of the categories.

In the inpatient group, males had an average of 3.28 admissions per patient while females had on average 4 admissions per patient. In consideration to the lengths of admissions without taking into account the average days of admission per patient, male patients had a statistically significant ($p=0.001$) higher average (155%) of 18.23 days ($\sigma=18.1$) than female patients with an average of 11.75 days ($\sigma=4.57$). This difference is slightly higher (157%, $p=0.01$) when we took into consideration the average number of admission days per patient. In this situation male patients had an average of 20.8 days ($\sigma=13.75$) and females had an average of 13.22 days.

In the inpatient group, female patients had 216% higher average hospitalization free days

(226 vs. 106 $p=0.003$). In the outpatient group, males had a non-statistically significant higher hospitalization free days (312 vs. 433 $p=0.1$).

Age distribution followed a left shifted normal distribution in all patient categories with an average of 36.7 years at the time of admission. We performed a regression analysis because we wanted to see if there is a pattern between the age of the patient and admission period in the inpatient group. There is a slight increase ($R=0.14$) of hospitalization duration in elder patients but the result is not conclusive because of few data points. Furthermore, this slight increase could be accounted by the fact that elder patients have additional somatic disorders that require medical attention.

Figure 4. Age and hospitalization period regression chart, $R=0.14$

We noticed 3 spikes in hospitalization period around patients aged 25-35 and we wanted to see if these were isolated cases of single patients or a more generalized trend. We performed another regression analysis, this time using the average hospitalization duration for each patient. The results in this

case show no correlation between age and hospitalization duration ($R=0.02$) and it showed that the first spike was produced by 3 out of 8 patients aged 24 to 26 while the second and third spike are singular cases of patients with an long average admission period (43 days and 57 days).

Figure 5. Average hospitalization days and age regression chart, $R=0.02$

Average hospitalization duration was 16.25 days ($\sigma=15.49$) and the average interval between hospitalizations was 143.93 days ($\sigma=174.89$) for the inpatient group. For the outpatient group, the average duration of hospitalization was 4 days ($\sigma=5.2$) and the interval between hospitalizations was 352 days ($\sigma=228.08$).

In the outpatient group, 11 patients received atypical antipsychotic treatment (64%) and 6 patients received typical antipsychotic treatment. We calculated the average day of admission between the groups and the results were 5.04 days of average hospitalization for patients receiving atypical antipsychotics and 1.33 days for patients receiving typical antipsychotics. The difference is statistically significant with a $p=0.003$. Oral antipsychotics were prescribed in 14 patients, the other 3 of the outpatient group received long action injectable antipsychotics (Depot). In this case, mean hospitalization period was on average 2.25 days for patients receiving Depot antipsychotics and 4.09 days for those receiving oral antipsychotics. The difference is not statistically significant with a p value of 0.07. Three patients received dual antipsychotic treatment. In this case the

average hospitalization days for those patients was 1, compared to 3.88 days for patients that received singular antipsychotic therapy ($p=0.001$).

In the inpatient group, 70% of the patients ($n=25$) received atypical antipsychotic treatment, 26% ($n=9$) received typical antipsychotics and 26% ($n=9$) received both typical and atypical antipsychotics. Mean hospitalization duration for patients receiving typical antipsychotics was 19.73 days ($\sigma=13.24$); 17.22 days ($\sigma=18.15$) for patients receiving atypical antipsychotics and 12 days ($\sigma=6.07$) for patients receiving both. Statistical significant differences were found for patients taking both typical and atypical antipsychotics versus patients taking atypical antipsychotics (12 days vs. 17.21 days, $p=0.01$) and versus typical (12 days vs 19.73 days, $p=0.02$). No statistically significant differences were found in hospitalization duration depending on whether or not patients received Oral vs Depot antipsychotics (16.07 days vs 15.33 days) or patients receiving a single antipsychotic agent or more (16.68 days versus 15.68 days).

Figure 6. Difference in average hospitalization period in the outpatient group depending on the type of antipsychotic treatment received

Figure 7. Differences in hospitalization days (inpatients) depending on the type of antipsychotic agent received.

Regarding the duration between admissions statistical significant differences ($p=0.008$) were found between patients receiving atypical antipsychotics (mean=161.83 days, $\sigma=161.13$) and patients receiving typical antipsychotics (mean=80.55 days, $\sigma=68.87$).

Patients receiving both typical and atypical antipsychotics had an average duration without admissions of 128 days but with very high variability $\sigma=228.89$ days, and no statistical significance compared to other groups.

Figure 8. Difference in hospitalization free days in patients receiving typical vs atypical antipsychotics

Statistically significant differences ($p=0.002$) in admission free days were found in patients receiving oral versus depot antipsychotics (170.55 days, $\sigma=168.85$ vs. 64.37 days, $\sigma=99.52$). We found this result contra intuitive and we wanted to see if there is any correlation between hospitalization duration and hospitalization free days in this population. We theorized that the lower admission free duration is because patients

came into the hospital to get their medication administered. A regression analysis showed that this is not the case as the majority of patients with admission free periods of around 30 days had admissions lasting between 5 and 12 days. No statistically significant difference was found in hospitalization free days between patients given a single antipsychotic agent and patients given two or more agents (147.5 days vs 139.7 days)

Figure 9. Regression chart. Horizontal axis: admission days, Vertical axis: admission free days. Polynomial trend line (continuous), Moving average line (dotted). $R=0.32$, $p=0.06$.

Figure 10. The difference in the inpatient group on hospitalization free days depending on the administration form of the antipsychotic drug.

Figure 11. Regression chart between hospitalization free days and the next hospitalization duration, inpatients. $R=0.1$.

DISCUSSION

A recent article published in July 2019 correlates the length of hospitalization for patients with schizophrenia and activity performance as it was measured using an adapted version of the Modified Barthel Index. (49) They have found that the optimal duration of hospitalization concerning increasing the global performance was between 20 and 50 days. The patients we

included in our study had a lower mean hospitalization of 16.25 days in the inpatient category, with an average of 144 days between hospitalizations. Although hospitalization free days are not a direct measure of symptomatic control, we consider it a good indicator, especially because we did not found a positive correlation between a short hospitalization free duration and the

following hospitalization duration. (Figure 10)

In the outpatient group, patients were observed for a shorter period if they had received a typical antipsychotic agent, which suggests that in the case of a mild symptomatic relapse in patients with hebephrenic schizophrenia, these agents could be beneficial over newer agents. The same was true for patients receiving more than one antipsychotic agent, either it being typical or atypical. Inpatients required fewer days of hospitalization if they received a combination of a typical and an atypical antipsychotic over either class on its own. Contrary to how outpatients performed, inpatients had a longer hospitalization period under typical antipsychotics than atypical, although not statistically significant. This result is more evident when considering hospitalization free days in the category of patients that received typical AP vs the category that received atypical AP. In this situation, the difference is double in the favour of atypical AP's. The most surprising correlation we made is the fact that patients receiving long lasting injectable antipsychotics had lower hospitalization free days, which might suggest that the treatment compliance to this class is not as high as it was thought to be. We looked to see if the lower hospitalization free days was due to the necessity of administering the

injection inside the hospital, expecting to see short hospitalization duration for those patients. As shown in figure 9, there is a group of patients that had admissions below the average, between 5 and 12 days that were admitted 30 days after the previous discharge. Even if we remove those patients from the analysis, we are still facing with 115 days of average duration between admissions which still is two thirds of what patients taking oral APs experience. We want to disclose that a number of variables could influence the results presented in this study. Firstly, this is a retrospective study and we cannot say that the type of medication that a patient received influenced the length of hospitalization and not otherwise, the hospitalization duration influenced the type of medication. This could especially be the case for the correlation between hospitalization free days and oral versus depot antipsychotic. In this case, there is a possibility that a number of patients with low compliance to oral treatment and high admission rates were switched to depot antipsychotics in order to increase the compliance, thus explaining the low hospitalization free days in the depot antipsychotic group. Secondly, the results are not conclusive due to the high variability of the data. In multiple cases the standard deviation for a certain data set was close to the average for that data set and in some cases, it exceeded the average.

CONCLUSIONS

1. Male patients had a higher number of hospitalization days both in the inpatient group (155% $p=0.001$) and outpatient group (274% $p=0.03$).
2. In the inpatient group, female patients had 216% higher average hospitalization free days (226 vs. 106 $p=0.003$). In the outpatient group, males had non-statistically significant higher hospitalization free days (312 vs. 433 $p=0.1$).
3. In the outpatient group, patients that received typical antipsychotics had fewer days of hospitalization than patients that received atypical antipsychotics (1.33 vs 5.04 $p=0.003$).
4. In the outpatient group, patients that received two or more antipsychotics had a lower average hospitalization than patients that received one antipsychotic (1 vs 3.08, $p=0.001$).

5. In the inpatient group, patients that received both an atypical AP and a typical AP had fewer hospitalization days than patients that received only one type of AP (12 vs 17.21 for atypical $p=0.01$, 12 vs 19.73 for typical $p=0.02$)
6. In the inpatient group, patients that received atypical APs had a higher average hospitalization free day than patients that received typical APs (80 vs 161 $p=0.008$)
7. Patients in the inpatient group that received depot APs had fewer average hospitalization free days than patients that received oral APs (64 vs 170 $p=0.002$)

These results are compiled from a population of just 53 patients and as such, although *p values* are indicative of acceptable statistical significance, averages are not highly suggestive due to the high variance represented in text but the standard deviance from the average (σ). Finally, we want to stress that although correlations were found between the type of antipsychotic agent and admission days and admission free days respectively, no correlations were found between the admission length and admission free length for patients receiving the same antipsychotic agent. Further investigations have to be made in order to obtain a higher statistical evidence level, including interventional studies.

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The authors declare that they have no potential conflicts of interest to disclose.

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Correspondence:

Tudor Florea,

MD, PhD stud, psychiatrist, “Socola” Institute of Psychiatry, Iași, Romania, no. 36 Str. Bucium,
tudor.cdflorea@gmail.com

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