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Effect of Atypical Anti-psychotics on Cognition in Schizophrenia

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Abstract:

Background: Schizophrenia is a chronic psychiatric disorder that affects mainly cognition and runs in chronic deteriorating course.

Objective: The study aimed to assess the cognitive function of schizophrenic patients compared to healthy control and verify the effect of atypical anti-psychotics on cognition in schizophrenia.

Patients & Methods: This case-control study included 3 groups, group 1: 20 newly diagnosed patients with schizophrenia, group 2: 20 schizophrenic patients receiving atypical antipsychotics and group 3: 20 control healthy persons. The participants of the three groups were subjected to clinical assessment, that included detailed psychiatric interview, neurological and general examination. Cognitive evaluation of both schizophrenic and control groups by, Wechsler Adult Intelligence Scale (WAIS), Wisconsin Card Sorting Test (WCST), stroop test (computerized version), the Trail Making test, continuous performance test and Wechsler Memory scale (WMS).

Results: The schizophrenic patients had worse results than healthy control group in all neuropsychological tests: The Wechsler Adult Intelligence Scale (WAIS), The Wisconsin Card Sorting Test (WCST), Stroop Test, The Trail Making Test (TM,(Continuous performance test (CPT) and The Wechsler memory scale (WMS).The impairment was more in the newly diagnosed patients without treatment.

Conclusions and clinical implications: Patients with schizophrenia suffered from cognitive impairment which mostly involved the different cognitive domains in different combinations, manifested least way in patients who received atypical antipsychotics.

Keywords: Atypical Anti-Psychotics, Cognition, Schizophrenia

key message: WHAT IS ALREADY KNOWN ON THIS TOPIC

Schizophrenia has been associated with profound and persistent cognitive impairment since the disorder was first identified by Emil Kraepel in 1896 and Eugen Bleuler in 1908. As a consequence, schizophrenia is associated with poor work record and low educational levels.

WHAT THIS STUDY ADDS

Severely impaired performance on different specific comprehensive cognitive tests is the strongest evidence for the importance of cognitive deficits in schizophrenia. In several cognitive domains, the average cognitive impairment in denovo schizophrenia patients can reach two standard deviations below the healthy control mean.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

Second-generation antipsychotic treatment may provide greater neurocognitive benefit to schizophrenia patients than first-generation, “typical” antipsychotics, so early diagnosis and proper treatment are essential measures.

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1.Background:

Schizophrenia progresses chronically if left untreated. Though the prevalence of the disease varies globally, estimates are that schizophrenia affects approximately 1% of adults, whereas prevalence in the US is 0.6% to 1.9% . Men are slightly more likely to be diagnosed and have an earlier onset than women, while African-Caribbean migrants and their descendants also have a higher incidence [1].Cognitive impairment is not unique to any subgroup of schizophrenia patients; it affects virtually every person with the disease [2].

Up to 98% of schizophrenic patients perform worse on cognitive tests than their parents' education level would predict [3]. All people with schizophrenia are likely to be functioning at a lower level than would be predicted in the absence of the disease [4].

Antipsychotics are still the gold standard in schizophrenia treatment. Antipsychotics are classified into two categories: typical or "first generation antipsychotics" (FGAs) and atypical or "second generation antipsychotics" (SGAs). Both drug categories function by blocking dopamine D2 receptors which is thought to be both essential and sufficient for antipsychotic effect [5, 6]. SGAs may have varying impacts on a wide range of schizophrenia symptoms. including not only positive and negative [7, 8], but also depressive symptoms, which are often poorly considered in clinical practice [9].

2. Objective:

The aim of this work was to assess the cognitive function in schizophrenic patients compared to healthy control for better assessment and understanding of this disorder, and verify the effect of atypical anti-psychotics on cognitive in schizophrenia.

3.Patients and Methods:

This case-control study was performed on 60 subjects collected from outpatient clinics and inpatient wards of Tanta University Hospital and Psychiatry, Neurology and Neurosurgery Centre, Tanta University in the period from September 2022 to June 2023 after approval of the Ethical Committee of the Faculty of Medicine at Tanta University (approval code: 35802/9/22). All participants and/or their first-degree relatives signed informed consent forms in this research after a full explanation of the benefits and pitfalls of the procedure.
Subjects in the present study included 3 group(Flowchart Figure 1):

Group 1: 20 newly diagnosed nonmedicated schizophrenic patients met Diagnostic and statistical manual of mental disorders (DSM) 5 criteria for schizophrenia.
Group 2: 20 schizophrenic patients receiving 2nd generation antipsychotic.
Group 3: 20 control healthy persons matching with the cases.

Inclusion criteria:

- Patients of schizophrenia who was diagnosed by DSM 5, both sexes, from 20 to 60 years.
- Any duration of illness including newly diagnosed patients.
- Educated, at minimum 12 years of education and same socioeconomic standard matched.

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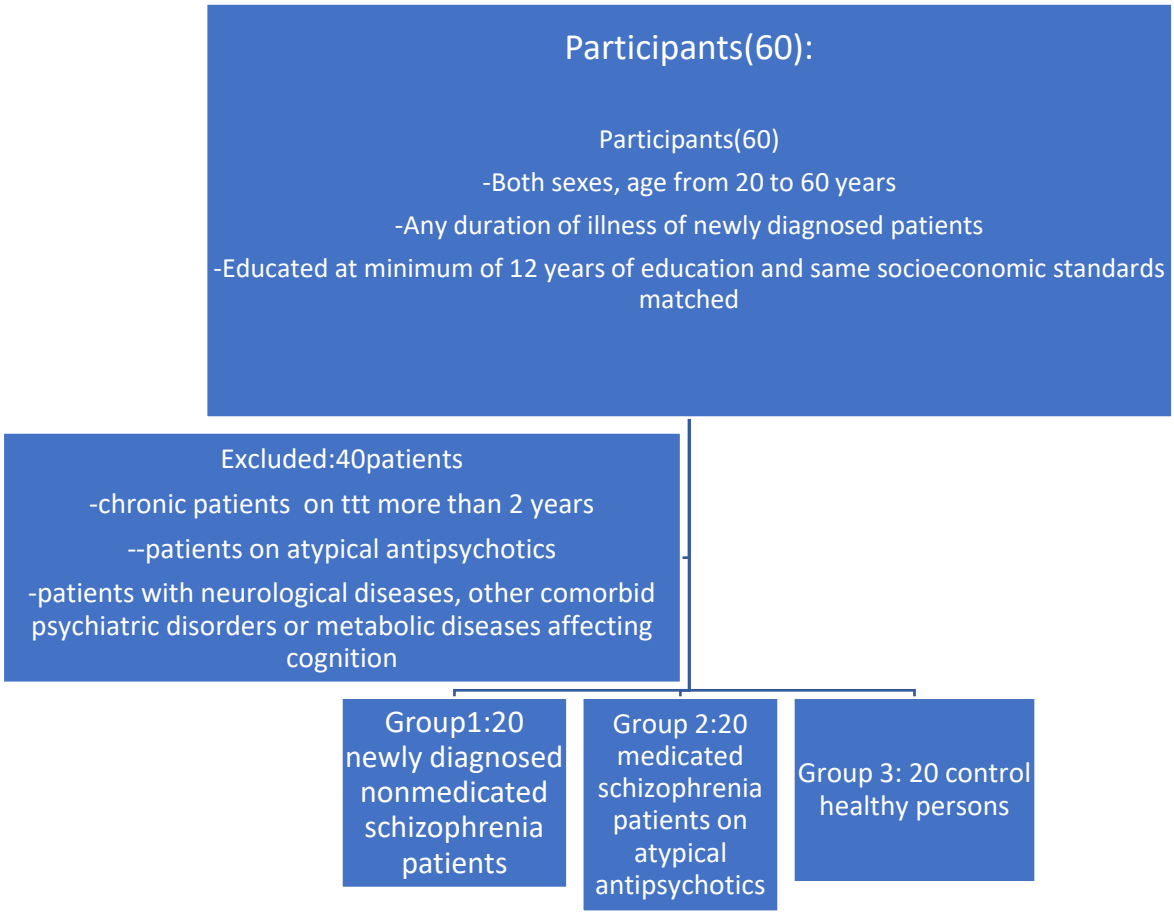
Exclusion criteria:

- Chronic patients of schizophrenia receiving treatment for more than 2 years.
- Patients taking typical antipsychotic and anticholinergic medications.
- Neurological diseases e.g., brain tumor and epilepsy.
- Other co morbid psychiatric disorders e.g., substance abuse.
- Metabolic diseases affect cognition e.g., liver failure and kidney failure.
- Intelligence Quotient (IQ) less than 90.



Flowchart figure 1:of participant enrollment

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The participants of the three groups were subjected to the following:

1. Clinical Assessment: included detailed psychiatric interview, neurological and general examination.
2. Psychiatric interview: structured psychiatric interview mini-international neuropsychiatric interview (MINI) was used for psychiatric interview of the participants. It involved comprehensive personal data, patient's complaint, present history, family history, educational history, occupational history, marital history, and the mental state examination. In the patient group, the treatment (the drugs which the patient was receiving at the time of examination) and the history of electroconvulsive therapy (ECT) application was inquired about for every patient. All these information were obtained by interview of the participants and their relatives.
3. Full neurological examination was performed to exclude cases with neurological illness. All the selected cases were having no localization or lateralization manifestation.
4. General examination: involved examination the head and neck, the chest and abdomen. The vital signs were reported.

Cognitive assessment:

All participants were evaluated by:

1. The Wechsler Adult Intelligence Scale (WAIS): is a test used to assess adult and adolescent intelligence. It is now in its fourth edition (WAIS-IV) [10].
2. The Wisconsin Card Sorting Test (WCST): a neuropsychological test of “set shifting.", i.e. the ability to be flexible in the face of changing reinforcement schedules. The WCST was written by David A. Grant and Esta A. Berg. Figure 2,3 **[11].**

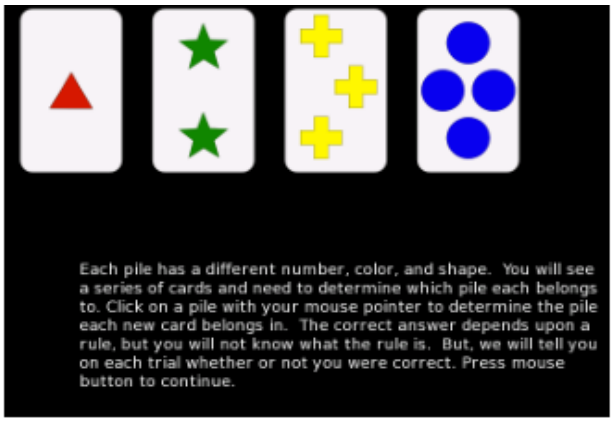

Fig2: Wisconsin card sorting test.

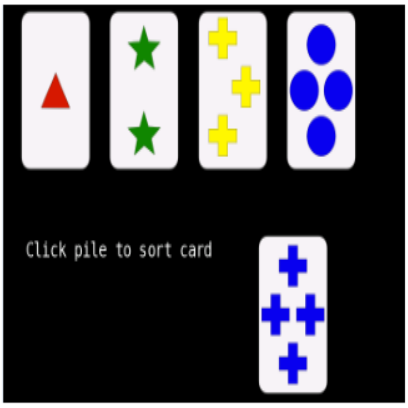

Fig3: Wisconsin card sorting test.

3. Stroop test (computerized version, Victoria-Stroop Task, Version 0.12): to test stroop effect (a demonstration of interference in a task's reaction time). Figure 4 **[12].**

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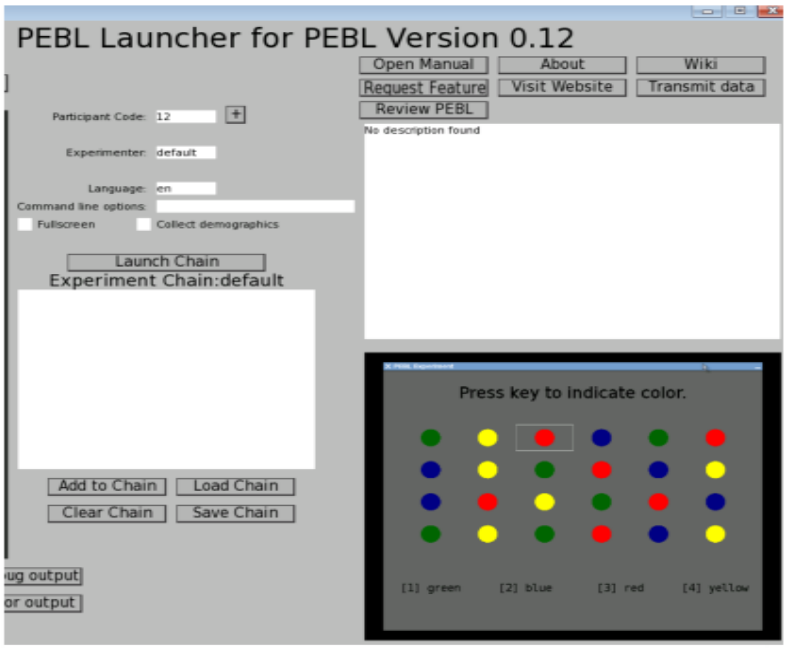

Fig3: Stroop test.

4. The Trail Making Test (Part A**,** Part B**)** : The Trail-making test is a visual attention and task switching neuropsychological test. The subject's goal is to complete the test as rapidly as possible, and the time it takes to do so is utilized to assess the primary performance. Supplementary figures 1,2 **[13,14].**
5. Continuous performance test (CPT) (computerized version): Several types of neuropsychological test that assess a person's sustained and selective attention [15].
6. The Wechsler Memory Scale (WMS) is a neurophysiological test used to assess a person's various memory functions. This test is eligible to anyone between the ages of 16 and 90. The fourth edition (WMS-IV), which was published in 2009 and was designed to be used with the Wechsler Adult Intelligence Scale IV, is the current version **[16].**

Statistical analysis of the data:

The IBM SPSS computer program bundle version 20.0. (IBM Organization, Armonk, NY) was utilized to look at the information that was provided into the computer. Number and percent were utilized to depict qualitative information. The Kolmogorov-Smirnov test was utilized to confirm the typicality of conveyance. The range, mean and standard deviation were utilized to depict quantitative information. The utilized tests were Chi-square test for categorical variables and the Understudy t-test: for ordinarily conveyed quantitative variables. F-test (ANOVA) for ordinarily disseminated quantitative variables, to compare between more than two groups, and Post Hoc test (Tukey) for pairwise comparisons. The importance of the procured results was assessed at a 5% level of noteworthiness. The degree of noteworthiness was received at $p<0.05$[17,18]

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4.Results:

Demographic results:

Regarding Age, there was significant difference in results between the 3 groups.Table 1
Regarding sex, there was not any difference in results between males and females. Table 1
Regarding smoking, there was not significant difference in results between the 3 groups. Table 1
Regarding education, In group 1 and 2 there was less cognitive impairment with higher education with no significant differences between the 3 groups. Table 1.

Table 1: Demographic data of the studied groups

	Control group No. (%)	**Group I** No. (%)	**Group II** No. (%)
Age in (years)			
Range	20 – 38	20 – 29	20 – 38
Mean ± SD	29.25 ± 6.81	24.35 ± 2.76	26.05 ± 4.90
P value	0.001*		
Post hoc test	p1=0. *, p2=0.999, p3=0.004*		
Sex			
Males	12 (60.0%)	13 (65.0%)	12 (60.0%)
Females	8 (40.0%)	7 (35.0%)	8 (40.0%)
P value	0.932		
Smoking			
Nonsmokers	14 (70.0%)	12 (60.0%)	14 (70.0%)
Smokers	6 (30.0%)	8 (40.0%)	6 (30.0%)
P value	0.435		
2ry education			
2ry education	7 (35%)	8 (40%)	7(35%)
High education	11 (55%)	11 (55%)	12 (60%)
Postgraduate	2 (10%)	1 (50%)	1 (5%)
P value	0.810		

Data are presented as mean ± SD and number of (%), *Significant as P value <0.05.Pair wise comparison between each 2 groups was done using Post Hoc Test (Tukey)

Cognitive assessment results:

Regarding WAIS, Schizophrenic groups had significantly lower score than control group and group II performed significantly better than group I. Regarding WCST, Correct response on WCST were significantly lower among both groups I and II than control and group I had lower performance than group II. Regarding Stroop test, Patients of group I had significantly higher score than both control and group II. Group II performed significantly better than group I and less than control group. Table 2

Table .

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Table 2: Comparison of WAIS and WCST correct responses among studied groups

	Control group	Group I	Group II
WAIS			
Range	99-119	88-103	94-110
Mean + SD	109.25±5.91	97.20±7.19	102.80±6.63
p	0.001*		
WCST			
Range	44-55	26-36	34-43
Mean + SD	49.83±5.36	31.47±7.49	39.97±8.17
p	0.001*		
Stroop test			
Range	112-446	410-560	290-564
Mean + SD	264.20±96.23	493.85±36.74	370.25±58.67
p	0.001*		

Data are presented as mean ± SD, WAIS: Wechsler Adult Intelligence Scale, WCST: Wisconsin Card Sorting Test, *Significant as P value <0.05.

Regarding trail making test part a, patients of group I had higher score than both control and group II. Group II performed better than group I and less than control group. While regarding trial making test part b, Patients of group I had significantly higher score than both control and group II. Group II performed significantly better than group I and less than control group. Table 3.

Table 3: Comparison of trail making test part a and part b among studied groups

	Control group	Group I	Group II
Trail making test part a			
Range	10-63	55-115	50-105
Mean ± SD	33.65±15.41	87.85±14.62	84.30±11.18
p	0.001*		
Trail Making Test part b			
Range	79-189	182-359	152-282
Mean ± SD	126.05±37.47	269.27±56.30	216.11±35.12
p	0.001*		

Data are presented as mean ± SD, *Significant as P value <0.05.

Regarding WMS, Schizophrenic groups had significantly lower score than control group and group II performed significantly better than group I. While regarding CPT, both group I and group II had poor performance on CPT and the difference was statistically significant. Table 4.

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Table 4: Comparison of WMS and CPT among studied groups

	Control group	Group I	Group II
WMS			
Range	81-125	73-91	79-105
Mean ± SD	106.65±9.86	80.55±5.39	94.40±6.48
p	0.001*		
CPT			
Range	281-355	240-310	271-318
Mean ± SD	323.55±22.36	269.26±16.99	291.53±12.37
p	0.001*		

Data are presented as mean ± SD. <0.05, WMS: Wechsler Memory Scale, CPT: Continuous performance test, *Significant as P value.

Regarding CPT correct responses, Schizophrenic groups had significantly lower score than control group and group II performed significantly better than group I. Regarding CPT errors, control group had significantly higher score than both group I and group II. Group II performed better than group I and less than control group. Supplementary table 1.

5.Discussion:

In assessment settings, Cognition had been found to be a predictor of community functioning in the real world as well as the capability to conduct activities of daily living. In cross-sectional and longitudinal follow-up studies, all of the core neurocognitive constructs had shown substantial connections to functional outcomes [19].

The schizophrenic patients in particular showed significant deficits in cognitive performance across various domains that include: learning, memory, attention, executive functioning, and processing speed. These cognitive deficits were associated with the outcome and social functioning in patients suffering from schizophrenia more than the positive and negative psychopathology. These cognitive deficits in schizophrenics often pre-date the illness onset and persist throughout the course of the diseases, and may be important in expecting the quality of life and the functional outcome [19]However, there had always been debate about the nature, selectivity and time of onset of these cognitive dysfunctions in relation to the onset of illness [20].

According to our results, Fujino et al., [21] presented premorbid IQ, Full Scale Intelligence Quotient (FSIQ), Verbal IQ, Performance IQ, the four indices, and the scaled scores of the WAIS-III subtests. All the IQ scales and scores of the four indices were significantly lower for the patients with schizophrenia than for the healthy controls (all Ps < 0.001). In contrast to a relatively small decline in premorbid IQ, the patients' FSIQ, Verbal IQ, and Performance IQ fell between 1.34 and 1.90 standard deviation below normal values .

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Performance IQ was 8.4 points underneath Verbal IQ within the patient group. Processing speed was markedly disturbed, being approximately 2 standard deviation below the healthy control group ($z = -2.16$, $d = 2.06$). Conversely, the three other index scores demonstrated a decline of approximately 1 standard deviation.

Our results were in accordance with those obtained by El Sawy et al,. [22] study WAIS result in schizophrenic patients was 82- 126 with Mean ± SD 103.07±9.19 and in control group was 89-136 with Mean ± SD 111.5±10.40. Besides, in El Sawy et al,. [21] study WCST number of preservative errors: in schizophrenic group was 8-24 with range 15.53±3.32 and in control group was 7-18 with range 12.58±2.63 and number of categories completed in schizophrenic group was 3-9 with range 5.76±1.27 and in control group was 5-10 with rang 7.68±1.30.

On the other hand Markela et al,. [23] showed that the analysis of the Stroop effect (incongruent– congruent) found no enhanced Stroop effect in patients ($t(1,28) = 1.5$, $p = .14$). The practice effects were not different between the groups. this may be due to they included two groups with lower number of participant. And this result was different from our study as both schizophrenic groups has lower performance than control group.

In a meta-analysis by Westerhausen et al,. [24], they agreed with our result as they reported that patients with schizophrenia had a greater Stroop interference effect in terms of response time (mean effect size: M(g) = 0.43; 95% confidence interval, CI95%: 0.35-0.52) and accuracy (M(g) = 0.62; CI95%: 0.47-0.77) measures of interference.

In agreement with Periáñez et al,. [25] study as they showed that there was significant differences regarding TMA between control and Schizophrenia patients. In El Sawy et al., [21] study trail making test b schizophrenic patients total time ranged from 73 to 120 with mean±sd 98.06±10.31 and time in control group was 59-100 with mean ± SD 79.79±10.13.

In agreement with our result Zhang et al [26] showed that in terms of CPT, there were substantial discrepancies between research groups. Our results didn't go with Zhang et al,. [26] as they appeared that there were insignificant differences between cases and groups with respect to brief time working memory this may be due to diverse patients' numbers and scales utilized.

Limitations: future studies would need to replicate the findings of the present work with a much larger sample size to understand the changes in cognition and effect of antipsychotics on cognition through the course. Follow up the cognitive profile of the patients after diagnosis and on the long run of the course of disease. Future research is needed to determine the relation between the reduced activity in certain brain areas functional magnetic resonance imaging (fMRI) and specific cognitive dysfunctions in schizophrenia.

6.Conclusion and clinical implications:

Schizophrenic patients performed significantly worse than the normal healthy control in about all the cognitive neuropsychological tests. Cognitive capacities influenced in schizophrenia incorporate verbal comprehension, perceptual reasoning, working memory, processing speed, cognitive flexibility, problem-solving, set-shifting of visual attention, task exchanging, selective attention, sustained attention, auditory memory, visual memory, visual working

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memory, immediate memory, and delayed memory. The net result would be that schizophrenia is related to a destitute work record and low educational levels. The newly diagnosed schizophrenic patients performed significantly worse than the patient's received 2nd generation antipsychotics.

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Abbreviations

CPT : Continuous performance Test
DSM: Diagnostic and Statistical Manual
SGAs : second generation antipsychotics
TM: Trail making Test
WAIS: Wechsler Adult Intelligence Scale
WM: Wechsler Memory
WCST: Wisconsin Card Sorting Test

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