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Comparing cognitive functions in medication adherent and non-adherent patients with schizophrenia

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ABSTRACT

Background: Medication non-adherence presents a considerable problem in patients with schizophrenia. Cognitive and executive functions can affect adherence. The association between medication non-adherence and cognitive impairment in schizophrenia is under investigated with limited and conflicting research data.

Purpose of the study: To prospectively assess the rate of drug adherence among a sample of patients with schizophrenia and to compare the cognitive and executive functions between adherent and non-adherent patients.

Subjects and methods: 109 patients with schizophrenia diagnosed according to the DSM-IV classification were initially assessed by the Wechsler Adult Intelligence Scale (WAIS), Wechsler Memory Scale-Revised (WMS-R) and Wisconsin Card Sorting Test (WCST) and six months later by the Brief Adherence Rating Scale (BARS).

Results: 68.8% were non-adherent to their antipsychotic medication. Adherent patients (31.2%) had significantly higher mean scores for the total, verbal and performance IQ. They had significantly higher mean scores in most of WMS subtests (orientation, information, verbal paired association, digit span, visual memory span), and higher mean scores for; total correct, conceptual level response, percentage and categories completed on the WSCT subscales ($P < 0.0001$). Whereas the non-adherent group had higher mean scores in; trials administered, total errors, perseverative responses, and perseverative errors ($P < 0.0001$). In a step regression analysis, digit span, conceptualization, total and percentage of errors were putative predictors of non-adherence.

Conclusion: Cognitive deficits, especially verbal memory and executive functions were the strongest patients' related factors associated with non adherence to medication. Psychiatrists ought to consider possible cognitive factors influencing adherence to enable offering proper interventions.

1. Introduction

Medication Adherence is defined as "the extent to which the patient's behaviour matches the agreed recommendations of the prescriber" (World Health Organization, 2003). While adherence is poor across a wide variety of physical and psychiatric conditions, the consequences of poor medication adherence can be devastating in schizophrenia, where the personal and societal costs of relapse are very high (Kirk Morton and Zubek, 2013). The consequences of medication non adherence can be detrimental for patients and their families in terms of personal suffering, poor functional outcome (Barkhof et al., 2012), higher relapse rate (Janssen et al., 2006), more health care utilization (Sun et al., 2007), increased rate of hospital admission (Knapp and Locklear, 2009) and poor quality of life (Dibonaventura et al., 2012).

Despite the development of new antipsychotics with broader efficacy and improved side effect profiles; nevertheless, the levels of medication adherence remain alarmingly low (Velligan et al., 2009).

Naturalistic studies pointed to high non adherence rates ranging from 25 to 50% (Lacro et al., 2002; Nose et al., 2003). A number of

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factors could be related to poor medication adherence among people with schizophrenia. These variables can be categorized into illness-related (Pinikahana, 2005), medication-related (Fenton et al., 1997), environmental-related factors (Owen et al., 1996), and patient-related factors (Moore et al., 2000). The latter include cognitive functions and individual's motivation for taking medication (Maeda et al., 2006).

The term cognition refers to the act of attending to stimuli in the environment and processing the information on several hierarchical levels. Cognitive functions include several domains mainly executive functions, memory, attention, vigilance, verbal tasks and social cognition (Burdick and Goldberg, 2008).

Cognitive deficits are thought to be a core feature of schizophrenia (Heinricks et al., 2013). Many studies have documented significant reduction of cognitive efficiency in patients with schizophrenia compared to normal subjects (Fioravanti et al., 2012; Bozikas et al., 2006; Zanelli et al., 2010; Lewandoweski et al., 2011a,b). These cognitive deficits involve impaired cognitive performance across a variety of measures as; executive function (Keefe and Harvey, 2012), memory function (Wobrock et al., 2009), vigilance and attention (Green et al., 2000), verbal fluency, psychomotor skills (Heinricks et al., 2013) and social cognition (Montreuil et al., 2010).

Cognitive dysfunction in schizophrenia can be a significant predictor of functional outcomes (Ziprusky, 2014) particularly global functioning, work performance, social skills acquisition and medication adherence (Hegde et al., 2013).

There are scarce and conflicting data on the association of cognitive impairment with antipsychotic non adherence (Buchanan et al., 1992; Jeste et al., 2003). Controversy still exists whether cognitive functions truly mediate functional outcome or may be related to medication non-adherence or service engagement (Johansen et al., 2011). Moreover, some investigators suggested that executive function (Maeda et al., 2006), memory impairment (Jeste et al., 2003), were strong predictors of adherence to medication, others, to the contrary, reported that non-adherent patients did better on tests of executive functions, verbal learning and memory, and having higher IQ than adherent patients (Yang et al., 2012, Jónsdóttir et al., 2013).

1.1. The rationale of the study

The relation between cognitive dysfunction and medication adherence was not previously studied in our region, however, research on other factors related to adherence to antipsychotic medication were previously investigated; as poor treatment satisfaction (Sweileh et al., 2012), patients involvement in folk therapy (El-Bahaey et al., 2005), insight and spiritually (Amr et al., 2013) or quality of life (Eticha et al., 2015).

The purpose of the study is to answer a basic question: Dose cognitive dysfunction relate to non adherence to antipsychotic drugs?

2. Material and methods

This is a prospective cohort study. The study was approved by the Ethical Committee of Ain Shams University, Egypt.

137 both male and female patients, aged between 18 and 50 years with the diagnosis of schizophrenia disorder according to the Diagnostic Statistical Manual of Mental Disorders 4th edition (DSM-IV) was preliminary recruited from the outpatient clinics of the Institute of Psychiatry, which is located at Eastern Cairo and serves both greater Cairo and the nearby governorates. Exclusion criteria were; history of drug dependence, past or present medical or neurological illness, head trauma, having IQ < 90 and receiving ECT before enrolment or during the follow-up period. Each patient signed a standard consent, after being informed about the nature and the confidentiality of the obtained information. The participation in this research was voluntary, and the participant has the freedom to withdraw at any time.

All enrolled patients underwent the following

1 **Confirmation of diagnosis** was done by senior clinical psychiatrists using the Research Version of the Structural Clinical Interview (SCID-I) (First et al., 1995). We used the Arabic version (El Missiry, 2003)
2 **Assessment of adherence** using: the Brief Adherence Rating Scale (BARS) (Byerly et al., 2008).

This is a pencil and paper clinician administered instrument used for assessing adherence to antipsychotic medications in patients with schizophrenia. The **BARS** provides valid, reliable, sensitive, and specific estimates of antipsychotic medication adherence with schizophrenia and schizoaffective disorder. The **BARS** consists of four items: three questions and an overall visual analogue rating scale to assess the proportion of doses taken by the patient in the past month to assess the patient's knowledge of their own medication regimen and episodes of missed medication taking, as follows: **1**. Number of prescribed doses of medication per day. **2**. Number of days in the past month when the patient did not take the prescribed doses. **3**. Number of days in the past month when the patient took less than the prescribed dose. The visual analogue scale rating is the key measure of adherence provided by the **BARS**. The BARS rating is reported as a percent of adherence (0%–100%), less than 70% indicate non adherence (Byerly et al., 2008). The BARS was rated by a clinical psychiatrists who were blind to the neuropsychological findings.

3. Assessment of cognitive functions

The assessment battery composed of tests relevant to cover intellectual abilities, memory and executive functions.

3.1. Wechsler Adult Intelligence Scale (WAIS)

The Wechsler Adult Intelligence Scale **(WAIS)** (Wechsler, 1981) is the most commonly administered general intelligence test for adults and is also viewed as a broad assessment of intellectual abilities. It is an individually administered measure of intelligence, intended for adults aged 16–89. It is the best standard and most widely used intelligence test in clinical practice and is intended to measure human intelligence reflected in both verbal and performance abilities. We used in this study the Arabic version of the **WAIS** by Melika (1996).

3.2. Wechsler Memory Scale-Revised (WMS-R) Wechsler, 1987 (Wechsler, 1987)

The Wechsler Memory Scale-Revised **(WMS-R)** is the most widely used instruments to assess memory functions in adults. It includes information and orientation questions, eight short-term memory tasks and four delayed recall trials, all of which take about 45 min to 1 h to administer. The subtests measure immediate and delayed components of verbal memory, verbal and figural stimuli, visual memory, immediate recall, episodic memory and visuospatial ability.

3.3. Wisconsin Card Sorting Test (WCST): we used the computerized version by Heaton et al., 2003 (Heaton et al., 2003)

The **WCST** was developed to assess the abstraction ability and

the ability to shift cognitive strategies in response to the changing environmental contingencies. It is considered a measure of executive function in that it requires strategic planning, organized searching, the ability to use environmental feedback to shift cognitive sets, goal-oriented behaviour and the ability to modulate impulsive responding. It provides information on several aspects of problem-solving abilities, and it is a measure of frontal lobe functions.

All assessments of cognitive functions were done by a trained neuropsychologist. Patients were assessed upon enrolment, followed up in the outpatient clinic for six months. All cognitive parameters were administered upon enrolment, while BARS after the six-month period.

28 patients were dropped out (one patient died, and 27 patients didn't attend the follow-up sessions or withdrew from the study), leaving a total of 109 patients who completed the study with 20.4% drop-out rate.

27.5% (N = 30) of patients were receiving typical antipsychotics, 65.1% (n = 71) treated with atypical antipsychotics. However, only 7.3% (n = 8) were receiving polypharmacy of typical and atypical antipsychotic medications. The overall prescribed dose of antipsychotics for all patients varied from 280 to 300 chlorpromazine equivalent as calculated using the standardized conversion formula (According to: Atkins M et al., 1997; Woods, 2003; Schatzberg et al., 2010).

4. Results

The patients' age ranged from 16 to 59 years (32.2 ± 9.0 years). 77 men (70.6%) and 32 women (29.4%) participated in the study. The majority of patients were single (68.8%, n = 57), while (24.8%, n = 27) were married and (6.4%, n = 7) were divorced. The majority of patients received only school education (61.5%, n = 67), (26.6%, n = 29) were university graduates and approximately 11.9% patients were illiterate. 57% were unemployed while 43% were engaged in different jobs. Patients' adherence assessed by the Brief Adherence Rating Scale **(BARS)** 6 months after enrolment, results revealed that about two thirds (68.8%, n = 75) of patients were non adherent while only one third (31.2%, n = 34) were adherent to their antipsychotic medications. Accordingly, we compared the adherent group with the non adherent group.

20.5% of the adherent patients (n = 2) received typical antipsychotics (Trifluperazine or Haloperidol) while the majority 70.5% (n = 24) received atypical antipsychotics (Olanzapine, Risperidone, Aripiprazol and clozapine) while 9% received polypharmacy from both groups in comparison to the non adherent group who were prescribed 30.7% (n = 23), 62.7% (47) and 6.6% (n = 5) typical, atypical and both types of antipsychotics drugs respectively.

Adherent patient received 20.6% typical antipsychotics, 70.6% atypical antipsychotics typical and atypical groups compared to 30.7%, 62.7% and 6.7% respectively of the non adherent group. The mean dosage of prescribed antipsychotic for the former group is 290.31 and for the latter, group is 288.72 chlorpromazine equivalent. Data illustrated in Table 1 shows that there are no significant differences elicited when comparing the two groups as regard; age, sex, and level of education.

4.1. Assessment of memory functions

The Wechsler Memory Scale Revised (WMS-R) revealed that adherent patients had significant higher mean scores in orientation, information, verbal memory; digit and visual memory span (Table 2). However, visual memory subscales didn't show any significant differences when compared among the two groups. Collectively, the results denote that the adherent group performed better on most of the subscales measuring memory functions. This can be interpreted that the memory impairment plays a role in non adherence to medication.

4.2. Executive functions

Data displayed in (Table 3) shows the results obtained by administration of WSCT. Results showed that the non adherent group had significant impairment in their executive functions. This group had higher significant percentage of errors and trials administered reflecting deficiency in attention and lower concentration abilities. They had more preservative responses indicating a specific deficit in cognitive flexibility. They scored significantly lower in percentage of conceptual level responses, reflecting lower abstraction and abilities to solve problems. Moreover, they obtained higher significant failure to maintain a cognitive set, denoting failure to use successful cognitive strategies.

4.2.1. Predictive cognitive factors correlated with non adherence

To evaluate the putative predictive value for the previously analyzed factors, we performed logistic regression analysis tests. We used patient adherence after six months as the dependent factor and used variables which showed statistical significance in the univariate analysis. The results as presented in Table 4 revealed that the most significant predictors of patients' non adherence were; memory impairment (especially digit span and visual memory span) and executive dysfunction (total errors, percentage errors and conceptual level response).

5. Discussion

Despite all the recent changes in antipsychotic pharmacotherapy and the plethora of international treatment guidelines recommending the long term antipsychotics treatment in patients with schizophrenia; however, medication non-adherence is still highly prevalent among those patients. Reviews of the literature report divergent rates of non-adherence, ranging from 20% up to 89% (Liberman et al., 2005; Liu-Seifert et al., 2012). Non-adherence can have a dire effect on the patient's illness control, quality of life, as well as the costs of health care (Barkhof et al., 2012).

Cognitive functions may be related to adherence behaviour; however, the relationship between cognitive dysfunction in schizophrenia and adherence to medication is still unclear. Perhaps due to the shortage of studies examining the association between adherence to medication and neuro-cognition (Jónsdóttir et al., 2013). We endeavoured to explore and compare cognitive and executive functions in a group of patients who adhere to their antipsychotics' regimen with those who didn't. We hypothesized that medication non adherent patients with schizophrenia would perform poorly on tests assessing cognitive functions as general intellectual abilities, memory and executive functions when compared to medication adherent patients.

In concordance with the previous studies (Jeste et al., 2003; Maeda et al., 2006), adherent group had higher significant scores in the verbal performance subscales and total IQ measured by the Wechsler Adult Intelligence Scale (WAIS), than did their non adherent counterparts. Our results reflected previous findings that patients with schizophrenia showed impairment of general cognitive abilities when assessed by traditional IQ measures (Hill et al., 2004; Wilk et al., 2005). This impaired performance reported to be pronounced at the first episode and remains fairly stable throughout late middle age (Hughes et al., 2003).

In our study we didn't use tools like using the National Adult Reading Test (NART) which is a test known to measure the premorbid IQ and the degree of deterioration (Nelson, 1982).

Table 1
Assessment of intellectual abilities in adherent versus non adherent patients.

Variable	Adherent group (n = 34)	Non adherent group (n = 75)	Test used	P Value
Gender:	n %	n %	X^2	
Male	19 (24.7%)	58 (75.3%)	4.61	.032
Female	15 (46.9%)	17 (53.1%)		
Education:	n %	n %	X^2	
Illiterate	2 (6%)	11 (15%)	12.67	.002
School education	16 (47%)	51 (68%)		
University graduates	16 (47%)	13 (17%)		
Age	Mean ± SD	Mean ± SD	t-Test	
	32.26 ± 8.6	32.28 ± 9.3	.008	.99
IQ (WAIS)	Mean ± SD	Mean ± SD	t-Test	
Verbal IQ	101.47 ± 12.2	84.89 ± 12.3	−6.52	.00
Performance IQ	97.67 ± 12.0	81.42 ± 10.2	−7.26	.00
Total IQ	98.73 ± 11.6	81.58 ± 10.4	−7.66	.00

Unfortunately, this test was not available in Arabic language in Egypt. Hence, it is still not certain whether the poor performance in IQ test detected predate the onset of illness.

There is still a chick-egg debate of whether the low IQ precedes the illness as a manifestation of an underlying neurodevelopmental disorder or is a consequence of it (Davies et al., 1998). Researchers in the field had conflicting views on the relationship between premorbid and current cognitive abilities. The premorbid level of performance issue remains both infrequently researched and unresolved. While Kremen et al. (2001) supported the deterioration hypothesis, on the other hand, Leeson et al. (2011) advocated the cognitive reserve hypothesis and proposed that those with higher premorbid intellectual function are more able to cope with the impact of neural insult either because of the higher brain structural reserve or because of better functional capacity to use compensatory forms of neural processing. Barnett et al. (2006) proposed that in schizophrenia, better cognitive reserve may result in fewer psychotic symptoms either because of superior reasoning skills or because of the ability to inhibit the abnormal neural processing that mediates psychotic symptoms. They also suggested that higher cognitive reserve would result in a better functional outcome because greater insight would lead to improved treatment adherence. This predicts that patients with higher premorbid IQ will have better outcomes with respect to both symptom remission and social function.

Memory impairment has been suggested to be a core cognitive deficit associated with schizophrenia as it is related to the ability to acquire different skills (Johansen et al., 2011). A possible reason for poor adherence to medication is memory deficit and poor ability to remember future intentions. Memory skills that are linked to everyday life skills (Zogg et al., 2010; Raskin et al., 2014) can play an important role in medication management abilities.

Memory functions encompass a number of abilities as measured by WMS-R, which assess both immediate and delayed components of verbal memory. Our results pointed to a significant better performance in subscales of WMS-R concerning orientation, information and verbal memory in adherent compared to the non adherent group. These results echo the findings of earlier studies pointing to the impairment in verbal memory and verbal learning that serves as a measure of immediate recall and recognition (Harvey and Keefe, 2001). This difficulty in encoding and then arranging information in the non adherent groups would make it difficult for them to handle social and interpersonal situations, including adherence to medication.

Jeste et al. (2003) concluded that cognitive functions, especially conceptualization and memory, were the strongest patient-related predictors of the ability to manage medications. Moreover, Donohoe et al. (2001) found that memory impairment was the variable which best discriminated the partial compliance.

In our study, we could not elicit differences in subtests measuring visual learning and visual memory when we compared the adherent with the non adherent group. This mirrors the finding of Gold et al. (2003) that visual memory correlates modestly with psychosocial rehabilitation as visual information is not easily expressed and that fewer tests are found to be sensitive to these deficits (Heinrichs and Zakzanis, 1998).

Executive functions encompass an array of cognitive processes that ultimately result in purposeful, goal-directed behaviour and are essential for dealing with activities of daily living. Non adherent patients exhibited poorer performance in subtests concerned with set shifting and cognitive flexibility as they scored higher in total errors, perseverative errors, the latter subtest result reflects the inefficient use of past contextual information and impairment in working memory (Orfei et al., 2010). Non adherent patients showed more trials administered, fewer categories completed and impaired task shifting ability, which reflects impairment in planning, problem solving, reasoning and conceptualization which may have impacted on their abilities to adhere to medical instruction. Moreover, in our study, the logistic regression analysis pointed that memory impairment especially digit span and visual memory span together with the deficit in executive functions in the form of higher percentage of errors, and impaired conceptualization were the strongest cognitive predictors of medication non adherence.

Table 2
Assessment of memory function in adherent versus non adherent patients.

Wechsler memory scale-revised subtest	Adherent group (N = 34)	Non adherent group (N = 75)	Test used	P Value
	Mean ± SD	Mean ± SD	t-Test	
Orientation information	13.52 ± 1.1	10.81 ± 2.6	−7.49	0.00
Verbal paired association 1	9.97 ± 3.2	8.22 ± 3.9	−2.41	0.01
Verbal paired association 2	4.41 ± 1.3	4.17 ± 2.3	−0.665	0.50
Visual paired association 1	8.00 ± 4.9	7.57 ± 3.6	−0.453	0.65
Visual paired association 2	3.84 ± 1.8	3.81 ± 2.0	0.404	0.68
Digit span	11.58 ± 4.2	6.42 ± 2.3	−6.64	0.00
Visual memory span	10.64 ± 2.9	7.06 ± 2.5	−6.08	0.00

Table 3
Assessment of executive functions in adherent versus non adherent patients.

Wisconsin card sorting test	Adherent group (N = 34)	Non adherent group (N = 75)	Test used	P Value
	Mean ± SD	Mean ± SD	t-Test	
Trials administered	96.79 ± 18.1	115.77 ± 20.5	4.621	.00
Total correct	70.35 ± 10.6	55.97 ± 14.7	−5.75	.00
Total errors	26.44 ± 22.0	59.80 ± 31.1	6.393	.00
Percentage errors	23.38 ± 17.5	48.29 ± 23.5	6.147	.00
Perseverative responses	20.97 ± 21.6	62.17 ± 40.3	6.916	.00
Percentage perseverative response	19.23 ± 16.0	50.33 ± 30.0	7.017	.00
Perseverative errors	17.64 ± 17.1	49.04 ± 30.3	6.859	.00
Percent perseverative errors	15.88 ± 12.4	39.16 ± 22.5	6.907	.00
Non perseverative errors	9.97 ± 8.3	10.76 ± 17.0	.257	.79
Conceptual level response	54.94 ± 27.0	38.61 ± 26.3	−2.97	.00
Percentage conceptual level response	62.73 ± 28.8	36.69 ± 28.1	−4.40	.00
Categories completed	5.23 ± 1.5	2.96 ± 2.2	−6.11	.00
Trial to complete first category	14.76 ± 7.8	38.48 ± 45.8	4.342	.00

These results were in concordance with previous findings that executive dysfunctions related to non adherence (Zanelli et al., 2010; Ziprasky, 2014) and may play a key role in medication management skills (Keefe et al., 2011; Wechsler, 1981).

To the contrary, Jónsdóttir et al. (2013) suggest that non adherent patients with schizophrenia performed better on neurocognitive tests than adherent group. The underlining mechanism of such findings wasn't interpreted by the authors and could be attributed to the use of different assessment tools and perhaps different inclusion criteria. Other researchers, as well as a systematic review by (Sendt et al., 2015), concluded that neurocognitive deficits were not related to non adherence (Yang et al., 2012, Mohamed et al., 2009; Lepage et al., 2010).

Despite debates, consensus guidelines (Velligan et al., 2009), went to support the finding that cognitive impairment is an important factor influencing medication adherence in patients with schizophrenia, related to everyday living (Orfei et al., 2010) activities and associated with low tendency to service engagement (Johansen et al., 2011). Moreover, Christopher and Harvey, 2006 stated that better executive functioning in schizophrenia may be associated with treatment success, while its impairments are associated with less engagement in therapy, medication compliance, and longer hospital stays. Furthermore, executive functions were found to be an important factor in determining motivation for medication adherence (Maeda et al., 2006) and is associated with medication competence (Na et al., 2015).

6. Conclusion

Cognitive deficits, especially verbal memory and executive functions featured as the strongest patients' related factors associated with the inability to manage adherence to the prescribed medication. Mental Health professionals should be aware of the possible impact of cognitive and executive functions deficit on adherence, and endeavour to assess these faculties and implement interventions to ameliorate these cognitive deficits aiming to enhance adherence to medication.

6.1. Implication

The results of this study support the need to develop and implement intervention that can improve adherence such as a adherence therapy (Anderson et al., 2010; Schulz et al., 2013 and Von Bormann et al., 2015), cognitive behavioural techniques

Table 4
Logistic regression test of potential predictive factors for adherence.

	B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
							Lower	Upper
Verbal IQ	.034	.121	.078	1	.780	1.034	.816	1.312
Performance IQ	.114	.106	1.142	1	.285	1.120	.910	1.380
Total IQ	.018	.206	.007	1	.932	1.018	.680	1.523
Verbal paired ass. 1	−.064	.206	.096	1	.756	.938	.627	1.405
Verbal paired ass. 2	−.150	.372	.164	1	.686	.860	.415	1.784
Visual paired ass. 1	−.007	.207	.001	1	.973	.993	.661	1.491
Visual paired ass. 2	−.068	.420	.026	1	.871	.934	.410	2.126
Digit span	1.023	.324	9.944	1	.002	2.781	1.473	5.250
Visual memory span	−.927	.336	7.616	1	.006	.396	.205	.764
Trials administered	−18.951	3.403E3	.000	1	.996	.000	.000	.
Total correct	19.338	3.403E3	.000	1	.995	2.504E8	.000	.
Total errors	−.038	.008	21.181	1	.000	.962	.947	.978
Percentage errors	−.417	.193	4.667	1	.031	.659	.452	.962
Preservative responses	.186	.775	.058	1	.810	1.205	.264	5.503
Percentage perseverative responses	−.218	.912	.057	1	.811	.804	.135	4.806
Preservative errors	18.892	3.403E3	.000	1	.996	1.602E8	.000	.
Percent preservative error	.479	1.511	.100	1	.751	1.614	.084	31.190
Non preservative errors	17.292	3.403E3	.000	1	.996	3.235E7	.000	.
Percent non preservative	2.828	1.520	3.464	1	.063	16.918	.861	332.587
Conceptual level response	−.130	.059	4.752	1	.029	.879	.782	.987
Percent conceptual level response	.085	.043	3.874	1	.049	1.089	1.000	1.186
Categories	−2.094	1.901	1.214	1	.271	.123	.003	5.110
Trial to complete	−.137	.122	1.251	1	.263	.872	.687	1.108

(Morrison et al., 2014), integrating pharmacotherapy and cognitive remediation (Medalia et al., 2014, Haddad et al., 2014) and psychosocial intervention (Macaluso and McKnight, 2013). However, these interventions should be sensitive to the individual patient's needs and cognitive abilities and there should be more evidence to determine the effectiveness of these specific interventions.

6.2. Strength and limitation

As far as we know, our study is the first research in Egypt aiming at studying the relationship between adherence to medication and cognitive dysfunction in a prospective study. The study is a part of a departmental project to unravel different factors related to non adherence including the severity of clinical symptoms, degree of psychopathology, insight and medication side effects.

The study is limited by the small size, thus, the results couldn't be generalized. A design that included healthy-control comparison for cognitive functions and adherence could have enriched the study. Furthermore, we could have had more insight by examining other factors as patients' attitude, believes towards medication, social cognitions, possible impact of stigma, and other possible socio-cultural barriers to adherence in the Egyptian culture.

Another limitation was not including the type and class of the prescribed antipsychotic medication in our analysis and not controlling for the possible effects of the antipsychotic medication on cognitive functions, especially first generation and sedating medication.

Our study did not address the socio-economic, cost and affordability factors that may influence adherence. Only typical antipsychotics were available for free in our Institute and those receiving atypical medication were self funding. This can limit the results interpretation and generalization.

Contributors

All the authors contributed equally to this work. Dr Rami Ali helped tremendously in the clinical assessment of patients and submissions to the Ethics and Research Committee. Mr. Abdel Gwad Khalifa, Clinical Psychologist performed all the neuropsychological testing. Dr. Mostafa Bastawy, Lecturer in Aswan University, did all the statistical analysis. Dr. Marwa Sultan, Associate Professor of Psychiatry helped in clinical assessments of some patients.

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Conflicts of interest

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