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Association Between Serum Anticholinergic Activity and Psychiatric Symptoms of Chronic Schizophrenia

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Abstract: The cholinergic system in schizophrenia has been associated with treatments, adverse effects, and pathophysiological processes. Although the role of the cholinergic system in schizophrenia has been thoroughly investigated, few studies have examined the dynamics of human cholinergic systems *in vivo*. We compared serum anticholinergic activity (SAA) in patients with schizophrenia to that in healthy controls and investigated correlations between anticholinergic activity and various domains of psychiatric symptoms. Fifteen chronically medicated patients with schizophrenia and 10 healthy controls participated in the study. We measured SAA using a receptor-binding assay ([^{3}H]-QNB). We also measured extrapyramidal motor symptoms and psychiatric symptoms, and assessed cognitive functioning with subscales of the Wechsler Memory Scale. Elevated levels of SAA (> 1.95 pmol / ml) were significantly more common among patients with schizophrenia than among healthy controls ($P < 0.001$). There was a significant negative correlation between SAA and extrapyramidal motor symptoms in patients with schizophrenia ($P = 0.043$). We found no significant association between SAA and other psychiatric symptoms and cognitive functions. These results indicate that SAA is greater among patients with schizophrenia than healthy controls, and that the anticholinergic effects might reduce extrapyramidal motor symptoms but exacerbate thought disorders. Further studies are warranted to confirm this finding in a larger cohort of non-medicated patients.

Key words: thought disorder, schizophrenia, acetylcholine, neurotransmitters, motor symptoms

Introduction

Schizophrenia is a severe chronic mental illness that affects about 1% of the population[1)]. Despite numerous studies over the past century, the etiology and pathophysiology of schizo-

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phrenia are poorly understood and the available treatments are only modestly effective[1]. Over recent decades, neuropsychopharmacological research has focused on identifying the role of neurotransmitter systems in schizophrenia. The disorder has been associated with deterioration of dopamine signaling and changes relating to other neurotransmitters, including glutamate, gamma-aminobutyric acid, serotonin, norepinephrine, and acetylcholine (ACh)[2].

ACh was the first neurotransmitter to be discovered. It operates in the central nervous system (CNS) and the peripheral nervous system (PNS). In the PNS, it acts in the parasympathetic nervous system, where it is involved in ganglionic neurotransmission and neuroeffector junctions, modulating various autonomic functions. It also acts in the somatic branch of the PNS, where it is involved in skeletal muscle activation. In the CNS, there are cholinergic interneurons and cholinergic projection neurons, mainly distributed in the frontal cortex, modulating motor function and cognitive abilities such as memory, executive function, and attention[3].

Antipsychotic agents used to treat schizophrenia, particularly first-generation antipsychotics, frequently cause extrapyramidal motor side effects such as tremor, akinesia, impairment of the postural reflex, akathisia, dyskinesia, and dystonia. Because these side effects lead to only modest impairments in activities of daily living, they are often treated with adjunctive anticholinergic agents to promote treatment adherence[4]. However, long-term use of anticholinergic agents can cause cognitive decline, delirium, and a worsening of psychiatric symptoms that is referred to as "antimuscarinic syndrome"[5], and thus, the use of anticholinergic agents has declined. Furthermore, second-generation antipsychotics that have reduced extrapyramidal side effects have been developed.

Recently, dysregulation of the cholinergic system in schizophrenia has been thoroughly investigated. Some researchers have suggested that the cholinergic system, especially muscarinic signaling, plays a key role in the pathogenesis of schizophrenia[6]. Although the role of the cholinergic system in schizophrenia has been suggested by pharmacological, physiological, and neuroimaging studies, few studies have examined the dynamics of human cholinergic systems *in vivo*. It is difficult to directly study cholinergic neurotransmission in the brain. However, it has been suggested that levels of serum anticholinergic activity (SAA) adequately reflect central anticholinergic activity[7]. There are few published studies of SAA measurement in patients with schizophrenia as a means of evaluating the effects of antipsychotic agents on motor symptoms or the effects of antimuscarinic agents on cognitive dysfunction. Furthermore, the association between SAA and motor symptoms has relied on the DiMascio Extrapyramidal Symptoms Scale[8], which does not provide a sufficient rating of extrapyramidal motor symptoms. Moreover, despite detailed investigations of various cognitive functions — for example, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS)[9] — detailed examination of clinical symptoms in neuropsychiatric and behavioral domains has not been conducted. Notably, levels of SAA and its association with physical and cognitive symptoms have not been directly compared between patients with schizophrenia and healthy controls.

In this study, we compared levels of SAA in older age patients with chronic schizophrenia with levels of SAA in healthy controls. We examined the association between SAA and various

domains of extrapyramidal motor symptoms and psychiatric and behavioral symptoms including affective symptoms, thought disorder, delirium, and deficit syndrome. We hypothesized that SAA would be negatively correlated with the severity of extrapyramidal motor symptoms, depressive symptoms, and negative symptoms, and would be positively correlated with the severity of thought disorder, delirium-related symptoms, and cognitive impairments.

Materials and methods

Participants

Fifteen chronic schizophrenia patients (six men and nine women) and 10 healthy controls (five men and five women) participated in the study. The two groups were matched for age. The participants with schizophrenia were either outpatients or inpatients at Showa University Karasuyama Hospital in Tokyo, Japan, and were diagnosed with schizophrenia according to the *Diagnostic and statistical manual of mental disorders, text revision, 4th edition*[10]. All participants were aged 60 years or older (mean ± SD : 65.5 ± 3.4 years ; range : 60–77 years). All those who had schizophrenia had an illness duration of more than 20 years (mean ± SD : 43.6 ± 7.49 years). No participant had any other significant neurological illness, or significant physical illness, history of drug misuse, other comorbidities, or comorbid personality disorders. The healthy controls were not taking any medication. Schizophrenia diagnoses and data on sociodemographic status were rechecked by two psychiatrists before the study. Participants were given the Japanese version of the National Adult Reading Test[11] to estimate their intelligence quotients (IQs).

Procedure

Serum Anticholinergic Activity (SAA)

Venous blood was obtained from participants between 7:00am and 9:00am. The blood was collected in untreated tubes and allowed to clot at room temperature for 30 min and then centrifuged at 2500 rpm for 10 min. Serum was removed and frozen at −80°C until it was assayed. SAA was measured according the protocol of Tune and Coyle[12], using a receptor-binding assay at LSI Medience Corporation, Kumamoto, Japan. In this radioreceptor technique, the amount of muscarinic antagonist, [^{3}H]-radiolabeled quinuclidinyl benzilate ([^{3}H]-QNB), inhibited by the blood sample is compared with that of a known concentration of atropine and expressed as an "atropine equivalent". The relationship between atropine concentration and [^{3}H]-QNB counts was linear for atropine concentrations ranging from 1.95 pmol / ml to 25 pmol / ml. Participants with SAA levels greater than 1.95 pmol / ml were defined as SAA positive[13].

Evaluation of Extrapyramidal Symptoms, Psychiatric Symptoms, and Cognitive Functioning

We evaluated the severity of global extrapyramidal symptoms among patients with schizophrenia using the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS)[14] and the Abnormal Involuntary Movement Scale (AIMS)[15], and we evaluated akathisia with the Barnes Akathisia Scale (BAS)[16]. The DIEPSS has been commonly used in Japan to evaluate drug-induced extrapyramidal symptoms since 1997 ; higher scores indicate more severe extrapyramidal symptoms.

We also evaluated the severity of global psychiatric symptoms with the Brief Psychiatric

Rating Scale (BPRS)[17] and the Positive and Negative Syndrome Scale (PANSS)[18]. We assessed affective symptoms with the Hamilton Rating Scale for Depression (HAM-D)[19] and the Young Mania Rating Scale (YMRS)[20]. We assessed delirium with the Delirium Rating Scale (DRS)[21], thought disorder with the Scale for the Assessment of Thought, Language, and Communication (TLC)[22], and residual symptoms with the Schedule for the Deficit Syndrome (SDS)[23]. In addition, we used the Global Assessment of Functioning (GAF) scale[24] to measure the general state of functioning and the Social and Occupational Functioning Assessment Scale (SOFAS)[25] to measure social functioning. Finally, we used the digit-span test and the immediate and delayed logical memory tests from the Wechsler Memory Scale (WMS)[26] to assess memory.

Data Analysis

Statistical analyses were performed using SPSS version 22 for Windows (IBM, Chicago, Illinois). SAA levels (defined as positive or negative) were compared between patients and healthy controls using the χ^2 test. Associations between SAA levels and all other scales were analyzed using Pearson correlation coefficients ($P < 0.05$ was considered significant).

Ethics Approval

The study was approved by the Ethics Committee of the Faculty of Medicine at Showa University. Written informed consent was obtained from each participant after a full explanation of the purpose of the study was provided.

Results

Characteristics of the schizophrenia patient group and the healthy control group are shown in

Table 1. Characteristics of patients with schizophrenia and healthy controls*

	Schizophrenia patients (n = 15)	Healthy controls (n = 10)	P value
Age (years)	66.2 (3.41)	65.5 (3.41)	0.70
Sex (male / female)	6 / 9	5 / 5	0.69
Education (years)	12.0 (2.32)	14.4 (2.37)	0.028
Estimated IQ	87.2 (10.1)	105.2 (18.4)	0.006
Chlorpromazine equivalent dose (27)	327.5 (386.6)		
Biperiden equivalent dose (27)	3.1 (2.7)		
PANSS			
Total	93.4 (17.6)		
Positive symptoms	18.8 (4.9)		
Negative symptoms	25.5 (4.2)		
General psychopathology	49.1 (10.6)		

*Data are mean (SD) unless otherwise indicated. IQ : Intelligence Quotient, PANSS : the Positive and Negative Syndrome Scale.

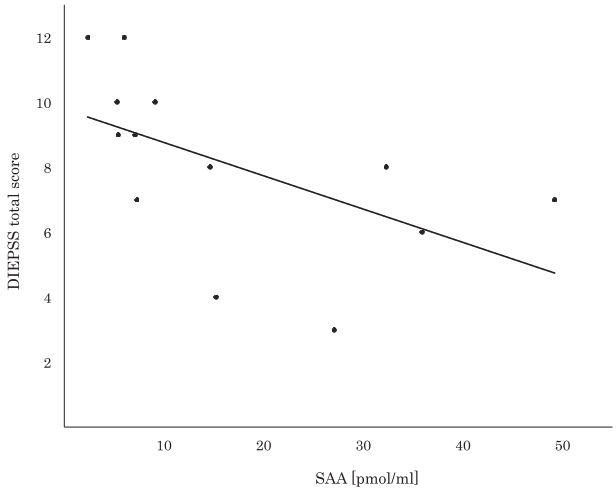
Table 1. There was no significant difference in age between the groups, but the sex ratio differed slightly. Education levels were higher for healthy controls than for schizophrenia patients, and estimated IQs were significantly lower for schizophrenia patients (mean : 87.2 ± 10.1) compared with healthy controls (mean : 105.2 ± 18.4).

For schizophrenia patients, the mean chlorpromazine-equivalent dose[27] was 327.5 mg (SD : 386.6 mg) and the mean PANSS total score was 93.4 (SD : 17.6), indicating moderately severe symptoms. Seven of the patients were receiving more than one antipsychotic drug and 11 were receiving anticholinergic agents (Table 1) to manage extrapyramidal side effects (mean ± SD

Table 2. Individual clinical status, medication characteristics and SAA levels of patients with schizophrenia

No.	Age	Sex	Age of onset	Illness duration (years)	PANSS	DIEPSS	SAA (pmol / ml)	Antipsychotic drugs	Chlorpromazine equivalent (mg) (27)	Anticholinergic drugs	Biperiden equivalent (mg) (27)
1	60	M	30	30	97	10	9.11	Quetiapine 450 mg	650	Biperiden 3 mg Trihexyphenidyl 4 mg Promethazine 100 mg	9
2	63	F	24	39	85	9	7.11	Blonanserin 24 mg, Risperidone 8 mg	1400	Biperiden 4 mg	4
3	69	F	19	50	70	3	27.1	Haloperidol 12 mg Levomepromazine 50 mg	650	Biperiden 2 mg	2
4	78	M	20	58	59	7	7.26	Bromperidol 3 mg	150	Biperiden 6 mg	6
5	64	F	24	40	84	6	35.9	Quetiapine 500 mg	800	Biperiden 3 mg	3
6	62	F	16	46	96	12	6.00	Bromperidol 12 mg Sulpiride 100 mg	650	Biperiden 4 mg	4
7	68	M	29	39	107	10	5.27	Paliperidone 3 mg	200	-	0
8	63	M	23	40	98	8	14.6	Haloperidol 6 mg Olanzapine 2.5 mg	400	-	0
9	61	F	28	33	97	10	< 1.95	Haloperidol 3 mg	150	Biperiden 4 mg	4
10	65	F	27	38	88	5	< 1.95	Aripiprazole 6 mg	100	-	0
11	77	F	22	55	93	9	5.42	Sulpiride 400 mg Chlorpromazine 50 mg	250	Trihexyphenidyl 2 mg	1
12	73	F	22	51	117	12	2.33	Risperidone 4 mg	400	Biperiden 2 mg	2
13	65	F	20	45	116	7	49.2	Quetiapine 750 mg Aripiprazole 3 mg	1100	Biperiden 6 mg Trihexyphenidyl 4 mg	8
14	62	M	18	44	118	8	32.3	Quetiapine750 mg	1100	-	0
15	64	M	18	46	77	4	15.2	Haloperidol 10 mg Risperidone 3 mg	800	Biperiden 4 mg	4

DIEPSS : Drug-Induced Extra-Pyramidal Symptoms Scale, F : female, M : male, PANSS : Positive And Negative Syndrome Scale, SAA : serum anticholinergic activity.



DIEPSS ; Drug-induced Extrapyramidal Symptoms Scale. SAA ; serum anticholinergic activity.

Fig. 1. DIEPSS total scores for SAA positive patients

biperiden-equivalent dose : 3.07 ± 0.8 mg) [27].

Individual patient data are shown in Table 2. The rate of positive SAA level (> 1.95 pmol / ml) was significantly greater among patients with schizophrenia compared with healthy controls ($\chi^2 = 11.11$, $P < 0.001$). Two of the healthy controls had a positive SAA level (2.00 pmol / ml, 2.31 pmol / ml) and eight had a negative SAA level (mean : 0.431 pmol / ml).

There was a significant association between SAA and DIEPSS total scores in patients with schizophrenia ($r = -0.568$, $P = 0.043$; Fig. 1). By contrast, we found no significant associations between SAA and the total scores of other measures (AIMS, BAS, BPRS, PANSS, HAM-D, YMRS, GAF, SOFAS, DRS ; Table 3). We analyzed the subscales of all of these measures and found significant associations between SAA and three subscales : "involuntary jaw movements" ($r = 0.74$, $P = 0.004$) of the AIMS, and "distractive speech" ($r = 0.56$, $P = 0.045$) and "tangentiality" ($r = 0.623$, $P = 0.023$) of the TLC. We found no significant correlations between performance on cognitive tests and SAA.

Discussion

We examined the association between SAA and the motor and psychiatric symptoms of chronic schizophrenia in older age. Medicated patients with schizophrenia exhibited greater SAA than healthy controls, and elevated SAA was significantly associated with less severe extrapyramidal motor symptoms. Most patients with schizophrenia in this study were medicated with anticholinergic drugs and / or antipsychotics with anticholinergic activity, thus our findings might not be generalizable to unmedicated patients with schizophrenia. However, some patients had relatively high SAA levels even without anticholinergic drugs (e.g., Table 2, patients 7 and 8). Previous studies have not compared SAA levels in patients with schizophrenia with those in healthy controls, and our results suggest that schizophrenia may involve a syndrome of exacer-

Table 3. Correlation coefficients for associations between SAA levels and all scores on the psychiatric symptom scales

	Mean (SD) score	r	P value
DIEPSS	8.076 (2.615)	−0.568	0.043
AIMS	0.769 (0.696)	0.364	0.221
BAS	2.461 (1.731)	−0.043	0.889
BPRS	48.461 (12.282)	0.290	0.336
PANSS			
Total	93.615 (17.665)	0.196	0.521
Positive symptoms	18.8 (4.982)	0.122	0.691
Negative symptoms	25.533 (4.208)	0.294	0.329
General psychopathology	49.133 (10.694)	0.033	0.914
HAMD	9.076 (5.075)	−0.151	0.622
YMRS	0.846 (2.142)	−0.074	0.811
DRS	0.769 (1.716)	−0.289	0.338
TLC	28.692 (15.208)	0.514	0.072
SDS	13.307 (3.337)	−0.194	0.526
GAF	36.153 (9.23)	−0.321	0.285
SOFAS	37.076 (9.972)	−0.392	0.185
Digit span			
Order	6.076 (3.689)	0.118	0.701
Reverse	3.153 (1.915)	0.005	0.987
Logical memory			
Immediate	1.461 (1.598)	0.118	0.700
Delay	1.115 (1.915)	−0.194	0.525

AIMS : Abnormal Involuntary Movement Scale, BAS : Barnes Akathisia Scale, BPRS : Brief Psychiatric Rating Scale, DIEPSS : Drug-Induced Extra-Pyramidal Symptoms Scale, DRS : Delirium Rating Scale, GAF : Global Assessment of Functioning, HAMD : Hamilton Rating Scale for Depression, PANSS : Positive And Negative Syndrome Scale, TLC : Scale for Assessment of Thought, Language and Communication Disorder, SAA : serum anticholinergic activity, SDS : Schedule for the Deficit Syndrome, SOFAS : Social and Occupational Functioning Assessment Scale, YMRS : Young Mania Rating Scale.

bated anticholinergicity to cope with the hypercholinergicity related to schizophrenia[6].

The correlation between extrapyramidal motor side effects in schizophrenia and SAA has only previously been reported using the DiMascio Extrapyramidal Symptoms Scale[28], which has been largely replaced by other measures such as the DIEPSS, AIMS, and BAS. We used these additional measures and showed for the first time a significant correlation between SAA and DIEPSS total scores (but not AIMS and BAS). The non-significant AIMS results suggest that anticholinergicity contributes little to the pathogenesis of tardive dyskinesia, which does not typically respond well to anticholinergic agents[29]. On the other hand, our results did not show a significant correlation between SAA and akathisia, which is frequently managed by anticholinergic agents. One reason for this non-significant result may be that the patients in our study were

in the chronic phase of schizophrenia and showed relatively non-severe akathisia (13 out of 15 patients scored less than 5 total points on the BAS).

Interactions between cholinergic and dopaminergic systems are critical for the regulation of motor control. An imbalance between striatal cholinergic (muscarinic) and dopaminergic functioning due to antipsychotic agents results in hypoactivity of the dopaminergic system and hyperactivity of the cholinergic system, and may contribute to extrapyramidal motor symptoms[30]. SAA is considered to be an indicator of net anticholinergicity, combining the effects of anticholinergic agents and endogenous anticholinergic activity[13]. Our results suggest that among patients with schizophrenia, elevated SAA may indicate and predict an inhibitory effect on the extrapyramidal motor symptoms except for involuntary movements.

The thought disorders included in the positive symptoms of schizophrenia affect patients' abilities to engage in activities of daily life and are related to poorer prognoses. We found that SAA was significantly correlated with the tangentiality subscale of TLC, but not PANSS and BPRS. Previous studies have suggested a possible positive association between anticholinergicity and specific psychotic symptoms known as "antimuscarinic psychosis". This type of psychosis includes tactile, visual, auditory, and olfactory hallucinations, hyperactivity, and severe disruption of thinking[5]. The association between SAA and TLC in this study suggests that such disruption-of-thinking aspects of schizophrenia may be exacerbated by anticholinergic toxicity, and, accordingly, decreased anticholinergic activity might reduce these symptoms. Thus, for patients with chronic schizophrenia and severe thought disorder who are being treated with antipsychotics and / or anticholinergic agents, it may be best to taper anticholinergic agents or antipsychotics with anticholinergic activity to reduce anticholinergic toxicity.

Although treatment with anticholinergic agents has previously been shown to result in a modest reduction in negative and depressive schizophrenia symptoms, our results showed no correlation between SAA and PANSS-negative scores, HAM-D scores, and DRS scores. Although these findings may be attributed to our small number of participants, it is possible that the negative and depressive symptoms of chronic-phase schizophrenia might not be influenced by anticholinergicity. This possibility should be addressed in future studies.

The individual patient data indicate greater SAA among patients taking quetiapine (Table 2, patients 1, 5, 13, and 14). This result agrees with the results of a previous study which suggested that patients taking clozapine, olanzapine, and quetiapine have greater anticholinergic activity than patients taking risperidone. Thus, we propose that clinicians pay careful attention to cholinergic side effects when prescribing second-generation antipsychotics with anticholinergic effects, especially quetiapine.

This study has several limitations. First, our sample size may have been too small to detect significant correlations between SAA and some measures, including TLC total score, negative symptoms, affective symptoms, and cognitive functions. Second, SAA levels were measured only once and therefore we could not investigate the effects of temporal changes in SAA among patients with schizophrenia. Third, how peripheral SAA reflects central SAA is uncertain. Future studies should determine the association between SAA and psychiatric symptoms by

including more participants and using a longitudinal design.

In summary, we showed that SAA was greater among patients with schizophrenia than among healthy controls, and that there was a significant negative correlation between anticholinergic activity and extrapyramidal motor symptoms (except involuntary movement and akathisia). Future studies should assess these trends with a larger cohort of non-medicated patients. In the future, SAA might be used to detect the optimal dose of psychoactive drugs in schizophrenia.

Conflict of interest disclosure

The authors have no conflict of interest to declare.

References

1) Harding CM. Course types in schizophrenia: an analysis of European and American studies. *Schizophr Bull*. 1988;**14**:633-643.
2) Keshavan MS, Tandon R, Boutros NN, *et al*. Schizophrenia, "just the facts": what we know in 2008: part 3: neurobiology. *Schizophr Res*. 2008;**106**:89-107.
3) Sitskoorn MM, Aleman A, Ebisch SJ, *et al*. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. *Schizophr Res*. 2004;**71**:285-295.
4) Broekema WJ, de Groot IW, van Harten PN. Simultaneous prescribing of atypical antipsychotics, conventional antipsychotics and anticholinergics — a European study. *Pharm World Sci*. 2007;**29**:126-130.
5) Yeomans JS. Role of tegmental cholinergic neurons in dopaminergic activation, antimuscarinic psychosis and schizophrenia. *Neuropsychopharmacology*. 1995;**12**:3-16.
6) Raedler TJ, Bymaster FP, Tandon R, *et al*. Towards a muscarinic hypothesis of schizophrenia. *Mol Psychiatry*. 2007;**12**:232-246.
7) Plaschke K, Thomas C, Engelhardt R, *et al*. Significant correlation between plasma and CSF anticholinergic activity in presurgical patients. *Neurosci Lett*. 2007;**417**:16-20.
8) DiMascio A, Bernardo DL, Greenblatt DJ, *et al*. A controlled trial of amantadine in drug-induced extrapyramidal disorders. *Arch Gen Psychiatry*. 1976;**33**:599-602.
9) Vinogradov S, Fisher M, Warm H, *et al*. The cognitive cost of anticholinergic burden: decreased response to cognitive training in schizophrenia. *Am J Psychiatry*. 2009;**166**:1055-1062.
10) American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 2000.
11) Matsuoka K, Uno M, Kasai K, *et al*. Estimation of premorbid IQ in individuals with Alzheimer's disease using Japanese ideographic script (Kanji) compound words: Japanese version of National Adult Reading Test. *Psychiatry Clin Neurosci*. 2006;**60**:332-339.
12) Tune L, Coyle JT. Serum levels of anticholinergic drugs in treatment of acute extrapyramidal side effects. *Arch Gen Psychiatry*. 1980;**37**:293-297.
13) Hori K, Konishi K, Watanabe K, *et al*. Influence of anticholinergic activity in serum on clinical symptoms of Alzheimer's disease. *Neuropsychobiology*. 2011;**63**:147-153.
14) Inada T. DIEPSS: a second-generation rating scale for antipsychotic-induced extrapyramidal symptoms: drug-induced extrapyramidal symptoms scale. Tokyo: Seiwa Shoten; 2009.
15) Guy W. Abnormal Involuntary Movement Scale (AIMS). In: ECDEU Assessment Manual for Psychopharmacology. Washington, DC: US Government Printing Office; 1976. pp 534-537.
16) Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry*. 1989;**154**:672-676.

17) Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychol Rep.* 1962;**10**:799-812.
18) Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;**13**:261-276.
19) Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;**23**:56-62.
20) Young RC, Biggs JT, Ziegler VE, *et al*. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry.* 1978;**133**:429-435.
21) Trzepacz PT. The Delirium Rating Scale. Its use in consultation-liaison research. *Psychosomatics.* 1999;**40**:193-204.
22) Andreasen NC, Grove WM. Thought, language, and communication in schizophrenia: diagnosis and prognosis. *Schizophr Bull.* 1986;**12**:348-359.
23) Kirkpatrick B, Buchanan RW, McKenney PD, *et al*. The Schedule for the Deficit Syndrome: an instrument for research in schizophrenia. *Psychiatry Res.* 1989;**30**:119-123.
24) Hall RC. Global assessment of functioning. A modified scale. *Psychosomatics.* 1995;**36**:267-275.
25) Morosini PL, Magliano L, Brambilla L, *et al*. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand.* 2000;**101**:323-329.
26) Wechsler D. Wechsler memory scale (WMS-III). 3rd ed. San Antonio: Psychological Corporation; 1997.
27) Inada T, Inagaki A. Psychotropic dose equivalence in Japan. *Psychiatry Clin Neurosci.* 2015;**69**:440-447.
28) Tune L, Coyle JT. Acute extrapyramidal side effects: serum levels of neuroleptics and anticholinergics. *Psychopharmacology* (*Berl*). 1981;**75**:9-15.
29) Klawans HL, Rubovits R. Effect of cholinergic and anticholinergic agents on tardive dyskinesia. *J Neurol Neurosurg Psychiatry.* 1974;**37**:941-947.
30) Scarr E, Gibbons AS, Neo J, *et al*. Cholinergic connectivity: it's implications for psychiatric disorders. *Front Cell Neurosci* (Internet). 2013;**7**:55. (accessed 2015 Mar 3) Availble from: http://journal.frontiersin.org/article/10.3389/fncel.2013.00055/full
31) Harrow M, Marengo JT. Schizophrenic thought disorder at followup: its persistence and prognostic significance. *Schizophr Bull.* 1986;**12**:373-393.
32) Tandon R, Mann NA, Eisner WH, *et al*. Effect of anticholinergic medication on positive and negative symptoms in medication-free schizophrenic patients. *Psychiatry Res.* 1990;**31**:235-241.
33) Tandon R, Greden JF. Cholinergic hyperactivity and negative schizophrenic symptoms: a model of cholinergic/dopaminergic interactions in schizophrenia. *Arch Gen Psychiatry.* 1989;**46**:745-753.
34) Chew ML, Mulsant BH, Pollock BG, *et al*. A model of anticholinergic activity of atypical antipsychotic medications. *Schizophr Res.* 2006;**88**:63-72.

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