

**SUPPLEMENTATION OF ARIPIRAZOLE IN RISPERIDONE
INDUCED HYPERPROLACTINEMIA: A DOUBLE BLIND
RANDOMIZED PLACEBO CONTROLLED TRIAL**

Submitted

By

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Dissertation submitted to

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY, CHENNAI,

In partial fulfillment of the requirements for the degree of

DOCTOR OF MEDICINE IN PSYCHIARY

Under the guidance of

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COIMBATORE – 2012

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled “**Supplementation of Aripiprazole in Risperidone Induced Hyperprolactinemia: A Double Bling Randomized Placebo Controlled Trial**” is a bonafide and genuine research work carried by me under the guidance of Dr. G. Raghuthaman, Prof and Head, Department of Psychiatry, PSGIMS & R, Coimbatore

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CERTIFICATE BY THE GUIDE

This is to certify that this dissertation entitled “**Supplementation of Aripiprazole in Risperidone induced Hyperprolactinemia: A double Blind Randomized Placebo Controlled Trial .**” is a bonafide work done by **Dr. Venkateswaran** in partial fulfillment of the requirement for the degree of M.D (PSYCHIATRY)

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INSTITUTION**

This is to certify that this dissertation **“Supplementation of Aripiprazole in Risperidone induced Hyperprolactinemia: A double Blind Randomized Placebo Controlled Trial.”** is a bonafide research work done by **Dr. Venkateswaran. R** under the guidance of **Dr. G. RAGHUTHAMAN**, Professor & Head, Department of Psychiatry, PSGIMS&R, Coimbatore.

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28.06.2010

To
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Department of Psychiatry
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Reference: Aripiprazole supplementation in Risperidone induced hyper prolactinemia: A randomized, double blind placebo controlled trial (Proposal No.: 10/186)

Subject: Ethics Committee approval for above referenced Study.

Dear Dr Venkateswaran,

We have received from you 16 copies of the documents related to your above study.

The members who attended the meeting held on 04.06.2010, at which your proposal was discussed are listed below:

Name	Qualification	Responsibility in IHEC	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
Dr V Ramamurthy	PhD	Chairman	Male	No	Yes
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Dr G Rajendran	D.M	Clinician	Male	Yes	No
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Dr Kezevino Aram	DCH, MSc (Harvard)	NGO	Female	No	No
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Dr T K Ponnusamy, Technical Advisor to Ethics Committee (AEM) was also present for the meeting.

We approve the trial to be conducted in its presented form and the validity of the approval is for one year.

The Institutional Human Ethics Committee expects to be informed about the progress of the study, any SAEs occurring in the course of the study, any changes in the protocol and patient information/informed consent, protocol deviations, requests annual study reports and asks to be provided a copy of the final report.

The Institutional Human Ethics Committee functions in accordance with ICH and GCP guidelines and those laid down in the Ethical Guidelines for Biomedical Research on Human Subjects by Indian Council of Medical Research New Delhi.

It is to be noted that neither you nor any of your proposed study team members were present during the decision-making procedures of the Ethics Committee.

Yours truly

for 
28/06/2010

Dr S Bhuvaneshwari
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PROJECT TITLE :

Aripiprazole supplementation in Risperidone induced hyper prolactinemia: A randomized, double blind placebo controlled trial

NAME OF THE INVESTIGATOR/S : Dr R Venkateswaran

NAME OF THE GUIDE/S : Dr G Raghuthaman

WAIVER OF CONSENT : No

REVIEW TYPE : Exempt

DATE OF THE MEETING : N/A

DECISION : Re-approved

APPROVAL DATE : 28.06.2011

VALIDITY OF THE APPROVAL : One year

CONTINUING PANEL REVIEW : Not Needed

Dr Y S Sivan
Member - Secretary
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At the outset, I thank the god for giving me the strength to perform all my duties.

It is indeed a great pleasure to recall the people who have helped me in the completion of dissertation. Naming all the people who have helped me in achieving this goal would be impossible, yet I attempt to thank a selected few who have helped me in diverse ways.

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Finally I thank my patients who formed the backbone of this study without whom this study would have not been possible.

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ABSTRACT

Objective: Hyperprolactinemia and related adverse effects often occur with antipsychotics, especially Risperidone. We investigated the effect of adjunctive treatment with Aripiprazole on hyperprolactinemia in patients with schizophrenia maintained on Risperidone.

Method: Thirty patients who were on stable doses of Risperidone were randomized either to get 10 mg of Aripiprazole or placebo in a double blind fashion. Serum prolactin levels were measured at the baseline and at the end of 8 weeks. Symptoms and side effects were assessed with the Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment for positive symptoms, Scale for Assessment of Negative symptoms, Simpson- Angus Rating scale, Barnes Akathisia Rating Scale, Arizona Sexual Experience Scale and Prolactin Related Adverse Event Questionnaire at baseline, weeks 2, 4, 6 and 8.

Results: Prolactin levels of patients receiving Aripiprazole significantly decreased compared to the placebo group, at the end of 8 weeks. In the Aripiprazole group, patients had 60.64% reduction in prolactin level at week 8 whereas no reduction was observed in placebo. Statistically significant reduction in scores of Arizona Sexual Experience Scale and Prolactin

Related Adverse Event Questionnaire were noted in Aripiprazole group which denote improvement in sexual side effects. No differences were observed on BPRS, Scale for the Assessment of Positive symptoms, Scale for Assessment of Negative Symptoms, Simpson-Angus Rating Scale, and Barnes Akathisia Rating scale scores were noted.

Conclusions: Adjunctive Aripiprazole treatment improved hyperprolactinemia in both gender, resulting in clinical improvement, with no significant effects on psychopathology and extra pyramidal symptoms. Partial agonistic property of Aripiprazole could be the cause of this observation.

BACKGROUND



SUPPLEMENTATION OF ARIPIPRAZOLE IN RISPERIDONE

INDUCED HYPERPROLACTINEMIA: A DOUBLE BLIND

RANDOMIZED PLACEBO CONTROLLED TRIAL

SCHIZOPHRENIA

Schizophrenia is the disorder of CNS characterized by positive symptoms, negative symptoms and cognitive symptoms. Positive symptoms include delusions, hallucinations and thought disorganization, negative symptoms includes loss of motivation and emotional vibrancy. (1) WHO report says “Schizophrenia is a severe form of mental illness affecting about 7 per thousand of the adult population, mostly in the age group 15-35 years. Schizophrenia affects about 24 million people word wide. (2).

It was postulated that abnormal dopaminergic activity and glutaminergic activity in the brain leads to pathogenesis of schizophrenia. Positive symptoms are due to increased dopamine activity in the meso limbic circuits. Negative symptoms are due to decrease in dopamine activity in the pre-frontal cortical neurons. Cognitive disturbances are mainly due to disturbances in Glutamate activity. (1)

Fig 1 shows key dopamine pathways in the brain.

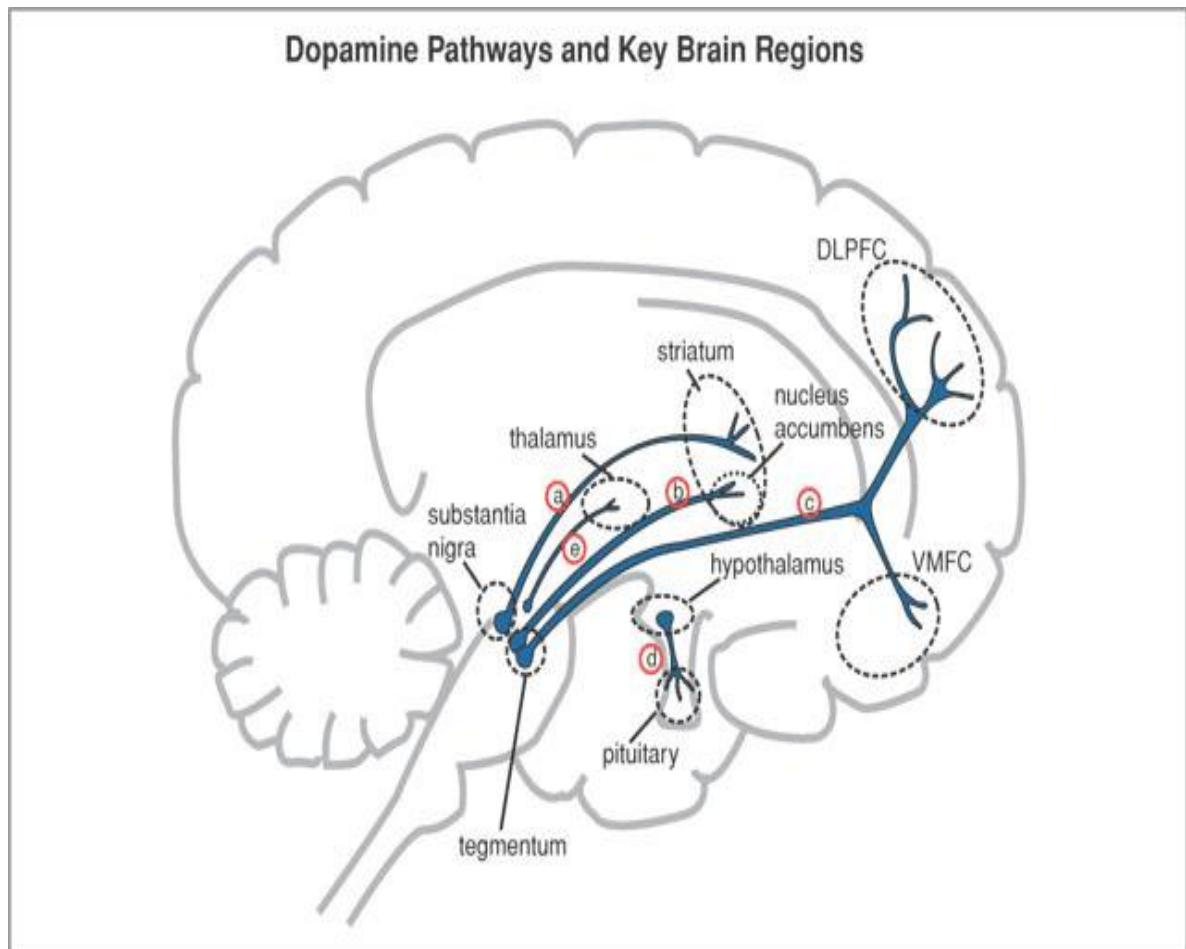


Fig - 1

ANTIPSYCHOTICS

Antipsychotic medications are the mainstay of treatment in schizophrenia. By blocking dopamine in certain regions of the brain they bring improvement in psychosis, but the same action in other parts of the regions results in unnecessary adverse reactions. (3)

Anti psychotic drugs causes reduction in dopamine activity in the Meso-limbic system which causes improvement in positive symptoms.

(Fig2)

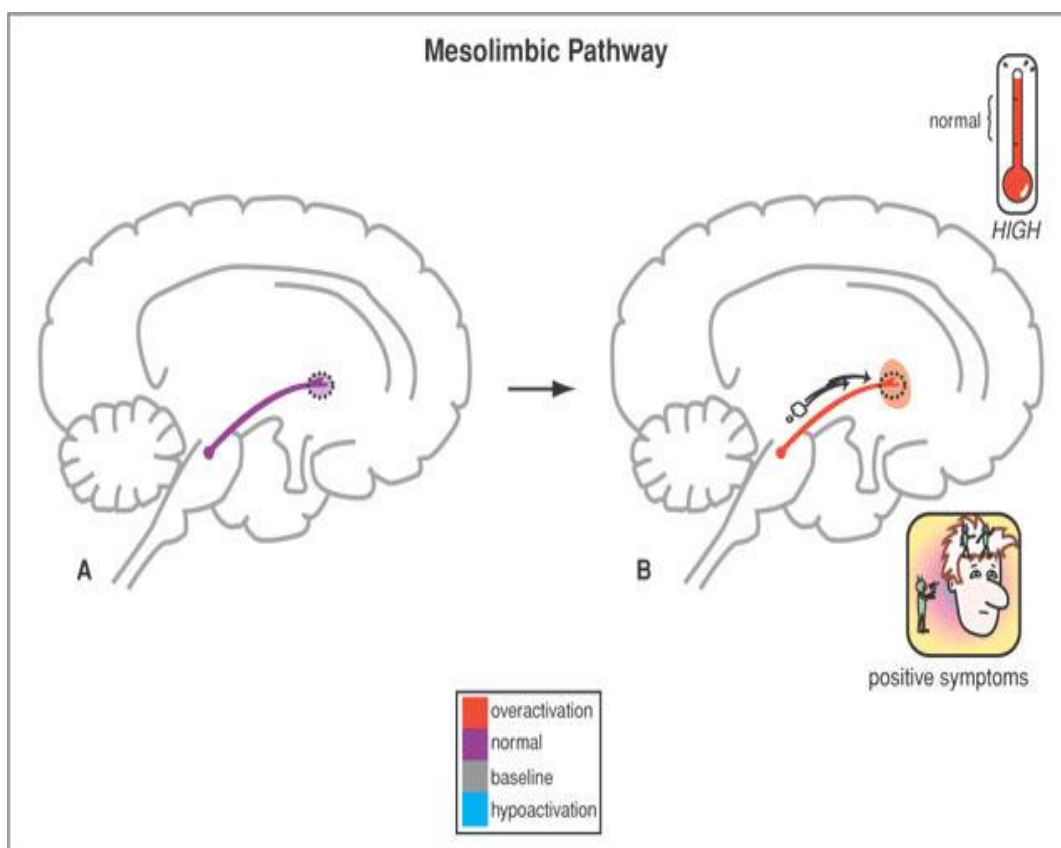


Fig - 2

Antipsychotics by blocking dopamine activity in Meso cortical pathway may add on to the cognitive as well as negative symptoms. (Fig 3)

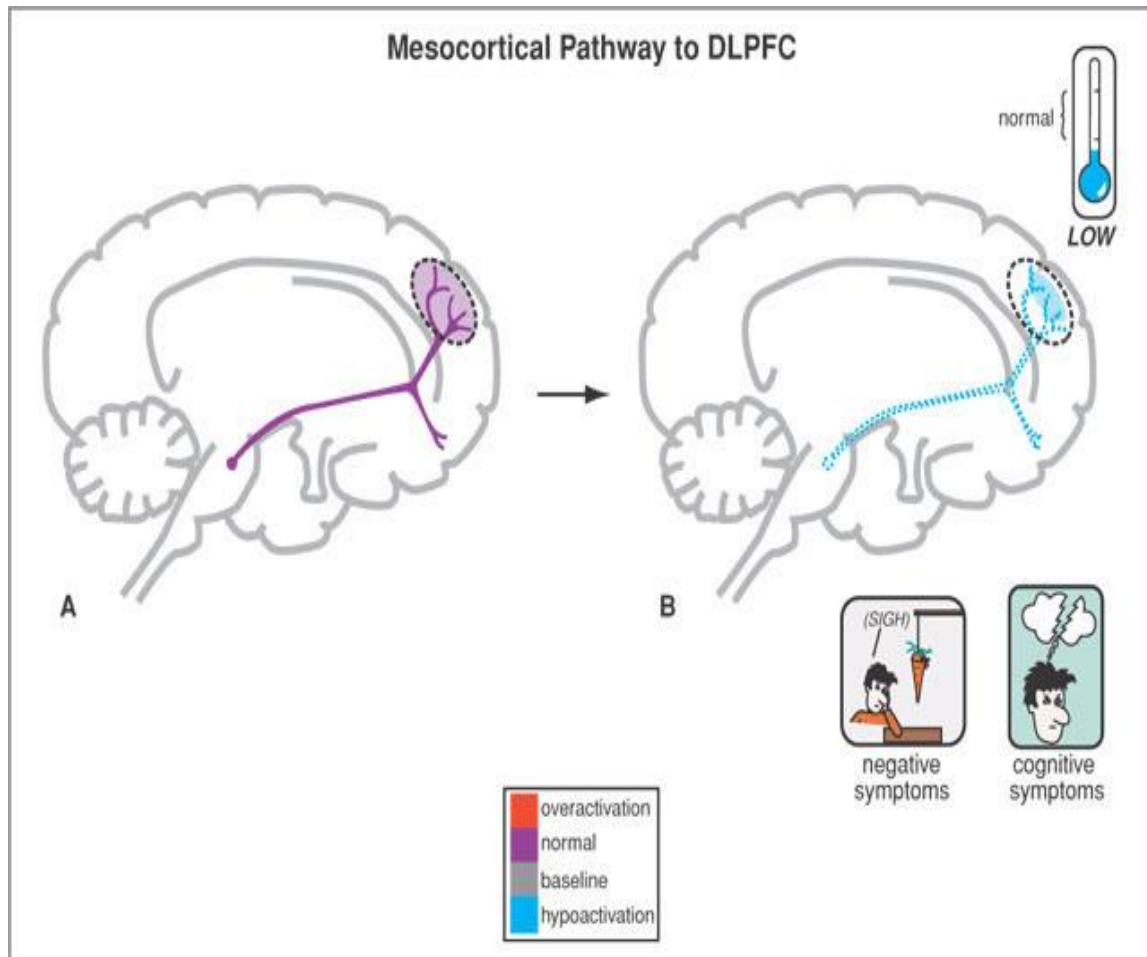


Fig - 3

The dopamine blockade action of antipsychotics in Nigro striatal dopamine pathway causes extra pyramidal side effects. (Fig 4)

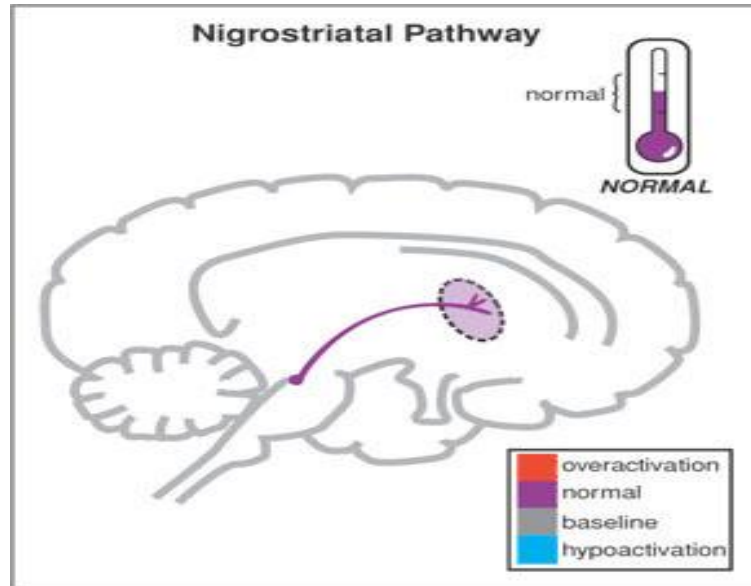


Fig - 4

Anti psychotics block dopamine in Tuberoinfundibular pathway which causes increase in serum prolactin level. (Fig 5)

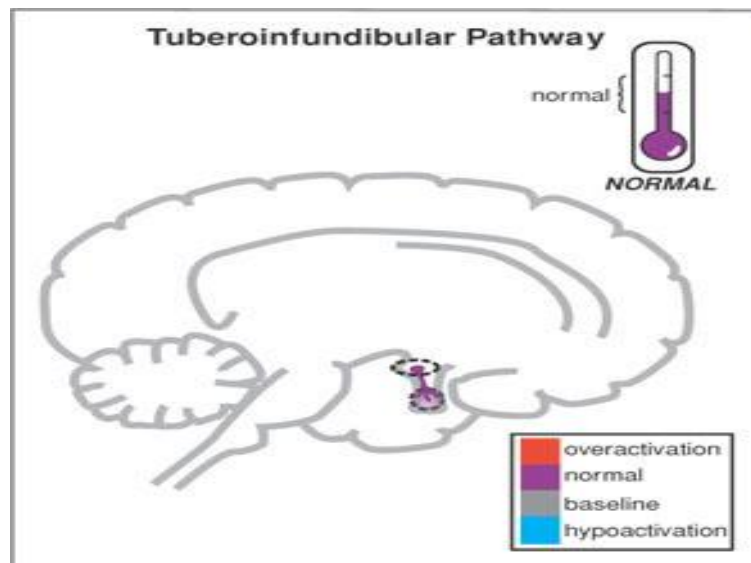


Fig - 5

ANTIPSYCHOTICS- CLASSIFICATION

Antipsychotics are classified into conventional or first generation antipsychotics and newer second generation antipsychotics. After the introduction of second generation antipsychotic there are so many studies published that showed these agents are superior to conventional antipsychotics in terms of efficacy especially negative symptoms and adverse effects. At the same time there are various studies that showed that there was no difference between first generation antipsychotics and second generation antipsychotics except Clozapine.(4) (5) Meta analysis done with the 148 trials with sample size of 18,272 patients showed that second generation antipsychotics are not a homogenous group. Agents like Olanzapine, Risperidone, Clozapine and Amisulpride are significantly better than conventional antipsychotic agents. (6)

However because of favorable side effect profile especially extra pyramidal side effects, second generation antipsychotics are commonly used first line agents clinically. (7)

Risperidone was the first second generation antipsychotic medication to be approved following clozapine. Risperidone is an atypical antipsychotic, widely available, relatively inexpensive and extensively used in India. Its efficacy has been well established in literature. CATIE trial says it is comparable with other second generation antipsychotics except clozapine

and first generation antipsychotic agents. (5) A Canadian multicenter study says that Risperidone has good efficacy in both positive and negative symptoms and superior over placebo. (8) It is widely used over the other second generation anti psychotics like Olanzapine because of lesser side effect profile in terms of weight gain, glycemic control and lipid profile. (9) Randomized control trial showed that risperidone was superior to olanzapine in terms of metabolic side effects and slightly better for positive and mood symptoms. (10)

However, Risperidone has its own unique side effect profile. Raised prolactin levels and its secondary complications may force the clinician to reduce the dose or change the medication. (11)

Antipsychotic drugs induced hyperprolactinemia and related morbidity is a neglected area in clinical practice as well as in research.

HYPERPROLACTINEMIA

Prolactin is a single chain polypeptide hormone consisting of 199 AA (23 k Da) stabilized by 3 sulphide bonds. Apart from lactation it is recently implicated in more than 300 physiological functions mainly related to reproduction and homeostasis. (12) It is secreted from the anterior pituitary gland. Prolactin receptors are found in almost all tissues and organs of the body. (13) Mechanisms that control the synthesis of prolactin are complex. It includes endogenous regulatory agents, feedback loops and circadian rhythm. It is also under tonic inhibition by the hypothalamus. This is mediated by number of factors of which Dopamine is very important. Dopamine is released by neuroendocrine cell of the tuberoinfundibular tract, reaches the lactotrophs through the portal system. Dopamine binds to D2 receptors on lactotrophs, receptor activation leads to inhibition of prolactin secretion. Disinhibition of lactotrophs by Dopamine antagonists (neuroleptics) results in increase in prolactin release. Persistent Disinhibition leads to elevated plasma concentration or hyperprolactinemia. (14)

Hyper prolactinemia suppresses gonadotropin-releasing hormone (GnRH), which in turn results in lesser gonadotropin release. This impairs gonadal steroidogenesis in both men and women. Hyper prolactinemia is associated with inhibited reproductive function and symptoms such as

galactorrhea, amenorrhea, gynaecomastia, erectile dysfunction, and anorgasmia. (15) (16) (17)

Antipsychotics induced hyperprolactinemia causes spontaneous galactorrhea of varying severity. It occurs more in women of premenopausal age group, who had children. It is very distressing side effect encountered by women. It is rare in male patients.

Amenorrhea occurs in about 30% of pre-menopausal women as a consequence of hyperprolactinemia due to risperidone. It may lead to potential negative consequences like increased risk of osteoporosis or neoplasia, discontinuation of treatment and worsening of psychopathology.

Patients with long term hyperprolactinemia have reduction in bone mineral density and osteoporosis. This is due to decrease in estrogen and testosterone secretion. In a study done with 45 patients with chronic antipsychotic use and high prolactin levels, there is decrease in bone mineral density measured from dual energy X-ray absorptiometry. This decrease in bone mineral density is secondary to hypogonadism due to increase in prolactin level. (18)

Approximately one-third of breast cancers are prolactin dependent, we don't know the influence of risperidone induced hyperprolactinemia on cancer prone patients. There are studies stating association of

hyperprolactinemia and breast cancer but it needs further prospective studies to establish causal relationship. (19)

Patients often underreport sexual dysfunction and majority of them discontinue treatment because of this sexual side effects. (20) One of the primary reasons of sexual dysfunctions is Antipsychotic induced hyperprolactinemia.

Among the antipsychotics Risperidone is associated with greatest increase in prolactin level, more than typical agents like Haloperidol. (21) Approximately 90% of the patients treated with Risperidone have raised prolactin level above base level. (15) (22) Possible explanation could be low penetration of Blood Brain Barrier (BBB) by Risperidone where pituitary gland lies outside BBB. (23) Side effects related to increased prolactin level are seen in 45% of the patients. (15)

Hyperprolactinemia- Management

Generally, three strategies have been recommended for the treatment of Risperidone induced hyperprolactinemia. Reduction of the antipsychotic dose, administration of adjunctive dopamine agonists, such as amantadine or bromocriptine and discontinuation of current treatment with switch to a different antipsychotic agent. These strategies, however can lead to other adverse consequences, such as worsening of psychotic symptoms, which may put the patient at a greater risk for adverse consequences, possibly worse than experiencing hyper prolactinemia itself. Relapse of psychosis can lead to adverse psychosocial consequences like losing skills to care, work and socialize, suicide, losing the job, marital disharmony, financial burden, hospitalization, care givers burden, etc. Switching to prolactin - sparing second generation such as Olanzapine, Quetiapine can be an effective treatment of hyper prolactinemia. However switching to these agents is not always possible in clinical practice especially if patient has already responded well and clinician/patient is unwilling to take risk on the clinical stability. Moreover medications like Olanzapine will produce other adverse effects like weight gain, excessive sedation, diabetes and cardiac abnormality. (24)

ARIPIPRAZOLE

Aripiprazole, a dopamine partial agonist, offers a novel, effective and well-tolerated treatment approach for patients with schizophrenia. Dopamine partial agonists are a new class of antipsychotic drugs. They have a lower intrinsic activity at receptors than full agonists, allowing them to act either as a functional agonist or a functional antagonist, depending on the surrounding levels of naturally occurring dopamine (neurotransmitter).

In the absence of a full agonist, partial agonists show functional agonist activity, binding to the receptor to produce a response. In the presence of a full agonist, partial agonists show functional antagonist activity.

Hence it should act as a functional antagonist in the mesolimbic dopamine pathway, where it blocks excessive dopamine activity and improves positive symptoms. It acts as functional agonist in the mesocortical pathway, where it improves reduced dopamine activity and thereby improving negative symptoms and cognitive impairment.

Aripiprazole should avoid the complete blockade of the nigrostriatal or tuberoinfundibular pathways, associated with extra pyramidal symptoms (EPS) and elevated prolactin levels, respectively. (25) Theoretically it should

increase dopamine concentration in tuberoinfundibular system, thereby it should improve hyperprolactinemia.

Aripiprazole has a good tolerability profile: no extra pyramidal symptoms, least sedating, minimal weight gain, minimal effects on lipids and glucose. (24) (26) (27) Aripiprazole has favorable effect on prolactinemia.

There are literatures which states, Aripiprazole reduces serum prolactin level due to its partial agonistic action as it increases Dopamine level in tuberoinfundibular system.

Adding Aripiprazole to an ongoing antipsychotic regime, just to treat hyperprolactinemia is an interesting area of research.

REVIEW OF LITERATURE



REVIEW OF LITERATURE

There are studies showing decrease in serum prolactin level even to normalization when Aripiprazole is used. (28) (29)

Vieta et al, sample size 347 compared Aripiprazole with haloperidol and found that there is no significant rise above baseline prolactin level in Aripiprazole group. (30)

In another randomized comparative trial, 83 patients with psychosis, where Aripiprazole was compared with risperidone, 93% in risperidone group had increased prolactin level whereas only 5% in Aripiprazole group.. (31)

Open label trial of changing to Aripiprazole for seven patients with symptomatic hyperprolactinemia due to atypical antipsychotic like risperidone, Amisulpride causes reduction in serum prolactin level up to 93.8%. (32)

In this RCT, (33) with 414 subjects, authors compared Aripiprazole 15 mg, 30 mg, with 10 mg Haloperidol or placebo. It was found there was mean reduction of 54.8% in Aripiprazole group whereas there is significant increase by 143% in haloperidol group.

In this study (34) with sample size of 262 patients with acute mania, authors compared Aripiprazole with placebo for efficacy and adverse effects. It is found that prolactin levels were reduced by 47.4% in 3 weeks.

Steven G et al, (35) with sample size 404 compared Aripiprazole 20 mg (n= 101), 30 mg (n= 101) with Risperidone 6 mg (n= 99) and placebo (n=103) in terms of efficacy and adverse effects and found that both the Aripiprazole group had a numerical decrease in serum prolactin level compared to the base line.

Meta analysis with 17 studies, of sample size 3,489 were given aripiprazole monotherapy, as an adjuvant to existing regime showed. aripiprazole lowered prolactin levelson an average of 74.3% across all studies. This effect is also seen even in psychotic patients with prolactinoma. Aripiprazole lowered prolactin levels by 59.3% in subjects with even normal baseline levels. Authors Concluded that aripiprazole may play an important role in treating psychiatric patients with hyper prolactinemia.. (36)

Marder et al, in a meta-analysis (37) with total sample size of 1,549, compared patients receiving 2 mg- 30 mg Aripiprazole (N = 932) , with patients receiving Haloperidol 5 to 20 mg (N = 201) and placebo and found that patients on Aripiprazole arm had mean reduction of serum prolactin level from the base line by 56.5 %(p < 0.001).

EVIDENCE FOR ARIPIPRAZOLE AS ADJUNCTIVE AGENT FOR TREATING HYPERPROLACTINEMIA

It was reported that in a patient with bipolar disorder maintaining on 150 mg of Haloperidol deconate , with symptomatic hyperprolactinemia when treated with adjunctive Aripiprazole up to 30 mg had reduction in prolactin level by 94% in spite of continuing Haloperidol. (38)

In a study (24), authors concluded that addition of Aripiprazole normalizes hyperprolactinemia in patients who were stabilized on haloperidol. Fifty-six patients with hyperprolactinemia taking haloperidol were enrolled. Haloperidol dose was fixed. Aripiprazole was dosed at 15 mg/day for the first 4 weeks, then 30 mg/day for the following 4 weeks. Prolactin levels of patients receiving Aripiprazole significantly decreased over time. In the Aripiprazole group, 88.5% of patients at week 8 had prolactin levels normalize compared to 3.6% of patients receiving placebo. Among 11 female patients with menstrual disturbances randomly assigned to Aripiprazole, seven patients regained menstruation during the study, whereas none receiving placebo did.

There is an open label prospective study with 19 patients where authors studied adjunctive treatment of Aripiprazole in patients maintaining

with risperidone causing reduction in serum prolactin level at the end of 8 weeks. (39)

There are case reports suggesting similar changes when Aripiprazole was added to Risperidone, (40)

It was reported that in 17 year old patient with Schizophrenia on Risperidone 4 mg and Depot Risperidone 25 mg bi weekly, with symptomatic hyperprolactinemia when treated with adjuvant Aripiprazole 15 mg, there was reduction of prolactin level from the baseline by 84.9%. (41)

But so far there is no randomized controlled study with Risperidone. As Risperidone has become one of the common atypical antipsychotics in treating schizophrenia, we need more research about managing Risperidone induced hyperprolactinemia.

AIMS

Aim of our research is to study:

1. Whether augmentation of Aripiprazole reduces serum prolactin levels and symptoms related to it in patients who are stable on Risperidone.
2. Our secondary outcome measures are to evaluate whether adjunctive Aripiprazole causes improvement in positive and negative symptoms of schizophrenia.
3. To study any emergent side effects to this augmentation.

INCLUSION CRITERIA

1. Patients in the age group of 15- 45, with the diagnosis of Schizophrenia according to Diagnostic and Statistical Manual IV TR.
2. Patient should be maintaining on the stable dose of Risperidone for at least 12 weeks.
3. Patients who are able to give written informed consent.

EXCLUSION CRITERIA

1. Patients on other oral/ DEPOT antipsychotics.
2. Patients having exacerbation of psychotic symptoms where dose Modification or change of antipsychotic agents is required.
3. Patients having adverse effect to current treatment regime which Requires dose modification.
4. Patients who have seizure disorder or other serious medical problems.
5. Patients who are pregnant or lactating.

TOOLS

1. A Structured Proforma to collect socio-demographic and clinical variables
2. Brief Psychiatric Rating Scale. (BPRS)
3. Scale for Assessment of Positive Symptoms. (SAPS)
4. Scale for Assessment of Negative Symptoms. (SANS)
5. Simpson-Angus Rating Scale for Extra pyramidal Side Effects.
6. Barnes- Akathisia Rating Scale.
7. Arizona sexual experience scale.
8. Prolactin Related Adverse Event Questionnaire.
9. Serum Prolactin assay in mIU/ ml by Sandwich principle.

BPRS

The BPRS (Overall and Gorham, 1962) is one the most widely used instruments for assessing clinical change in psychiatric patients. It has 18 items, a seven-category dimension of severity, ranging from 0 (not present) to 6 (extremely severe). The available evidence suggests that the BPRS is both valid and reliable in assessing the psychopathology. The median inter-rater reliability scores across the 18 items of the scale are reported to range between .63 and .88. (42) (43)

Scale for the Assessment of Positive Symptoms (SAPS) and Scale for assessment of negative symptoms

SAPS and SANS were designed to provide detailed assessment of positive and negative symptoms of schizophrenia. Domains in SAPS include hallucinations, delusions, bizarre behavior and thought disorder. SANS include affective flattening, poverty of speech, apathy, anhedonia and inattentiveness. Each instrument contains 30 fully anchored items. Each item has rating from 0 to 5. The total scores ranges from 0 to 150 for each instrument. Good to excellent interrater reliability has been demonstrated for each instrument. Each scale has high internal consistency. Validity is supported by correlation with other symptom severity instruments. These scales provide comprehensive characterization of symptomatology. (44)

Barnes Akathisia Rating Scale

This is the rating scale for drug-induced akathisia. It contains diagnostic criteria for pseudoakathisia, and mild, moderate, and severe akathisia. It includes items for rating the observable, restless movements which characterize the condition, the subjective awareness of restlessness, and any distress associated with the akathisia. There is also an item for rating global severity. The inter-rater reliability for the scale items (Cohen's κ) ranged from 0.738 to 0.955. (45)

Simpson Angus Rating Scale for Extra pyramidal side Effects

It was developed to monitor the side effects of antipsychotic agents. It contains ten items. Each item is rated on a five point severity scale ranging from 0-4. Scores are reported as mean on all the 10 items with .3, as upper limits of normal. It focus on parkinsonian symptoms especially rigidity. It has good reliability and validity. This scale is used widely in clinical and research settings. (46)

Arizona Sexual Experience Scale (ASEX)

The Arizona Sexual Experiences Scale (ASEX) is a five-item rating scale that quantifies sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. Total scores range from 5 to 30, with the higher the score, more severe the sexual dysfunction. It has high positive and negative predictive value. ASEX has excellent internal consistency and scale reliability ($\alpha = .9055$). The ASEX also has strong test–retest reliability. It is more valid and sensitive tool to measure sexual dysfunction. Other advantages include the questions are short, easy to understand, easy to score and interpret. (47)

Prolactin Related Adverse Event Questionnaire

It is a scale developed to objectively measure adverse events related to hyperprolactinemia. It has three main items, menstrual disturbances, chest symptoms and penile functions. There are 3 sub items in menstrual irregularity, 5 sub items in chest symptoms and 4 sub items in penile function. Each sub items have severity ranges from 0-5, with higher the score more the severity.

Prolactin Measurement

It is measured by ECLIA- Electrochemiluminescence Immuno assay. This is based on the principle called quantitative sandwich immunoassay. The minimal detectable concentration of human Prolactin by this assay is estimated to be 1.5 ng/mL. This kit exhibits no detectable cross-reaction with human FSH, LH, and TSH, hCG and hGH. This immunoassay is calibrated against WHO, 3rd IS, 84/500. In this assay, no hook effect is observed up to 10,000 ng/mL. The monoclonal antibodies used are highly specific against prolactin.

Patients are asked to give early morning fasting sample and also asked to be abstinent from sexual intercourse or any kind of stimulation of breast on the previous night.

SAMPLE SIZE CALCULATION

Shim et al, 2007 (24), found that haloperidol (20 to 25mg) causing a mean increase of prolactin level by 94.5 (SD 38.1) ng/ml. Earlier studies have found that risperidone 6mg causing similar increase in the prolactin level. Extrapolating these estimates, in this study, we hypothesize that there would be > 50% fall in the prolactin levels in Aripiprazole group than placebo group. To detect this, keeping alpha at 0.05, power of the study 80 and expected drop out rate at 30%, we needed 15 patients in each Aripiprazole and placebo groups.

METHODOLOGY



METHODOLOGY

We screened all the patients who were attending our department since January 2010. Patients who met the eligible criteria were included. We administered Structured Clinical Interview for DSM disorders and only patients who fulfill the Diagnostic and Statistical Manual of Mental Disorders IV TR criteria for schizophrenia were included in the study. We explained in detail about the project to the patients and his/her key family members accompanying the patient and obtained written informed consent from the patient. Totally 30 patients were recruited into the study.

Randomization

We did stratified block randomization so that we get equal male and female patients in the Aripiprazole and placebo groups. (Literature shows that incidence and effects of hyperprolactinemia differs between males and females). (24)

Medications and Blinding

PSG College of pharmacy prepared placebos looking similar to Aripiprazole (10 mg) tablets and packed them separately. Aripiprazole and placebo tablets were labeled as Drug A and Drug B for masking and the primary investigators and patients were blind to the medications thought out

the study. PSG College of pharmacy officially maintained the blinding till the completion of the study.

At the baseline we used Brief Psychiatric Rating Scale (BPRS), Scale for the assessment of positive symptoms (SAPS), and Scale for the assessment of negative symptoms (SANS) to assess the severity of psychopathology. Simpson-Angus Rating Scale for Extra pyramidal Side Effects and Barnes akathisia scale to monitor extra pyramidal symptoms.

To assess the sexual dysfunctions we used Arizona sexual experience scale at the baseline and also we assessed menstrual irregularities and galactorrhea using Prolactin Related Adverse Event Questionnaire.

Prolactin level was done from the morning fasting blood at the baseline.

Patients were followed up for 8 weeks after baseline assessments. Each patient was given a sachet containing either Aripiprazole or placebo (both looking identical), 2 weeks at a time, and patients came once in 2 weeks to collect the medications. At the end of every two weeks we repeated the BPRS, SAPS, SANS, AIMS, sexual dysfunctions questionnaire, Prolactin Related Adverse Event Questionnaire.

At the end of 8 weeks, we repeated BPRS, SAPS, SANS, AIMS, sexual dysfunctions questionnaire, Prolactin Related Adverse Event Questionnaire and did fasting prolactin level.

Study was funded by ICMR and PSGIMSR. Study protocol was approved by institutional ethics committee of PSGIMSR.

HYPERPROLACTINEMIA

It is defined as the elevation of serum prolactin level above 324 IU/ ml in male patients or more than 496 IU/ ml in female patients. (Our lab reference)

STATISTICAL ANALYSIS

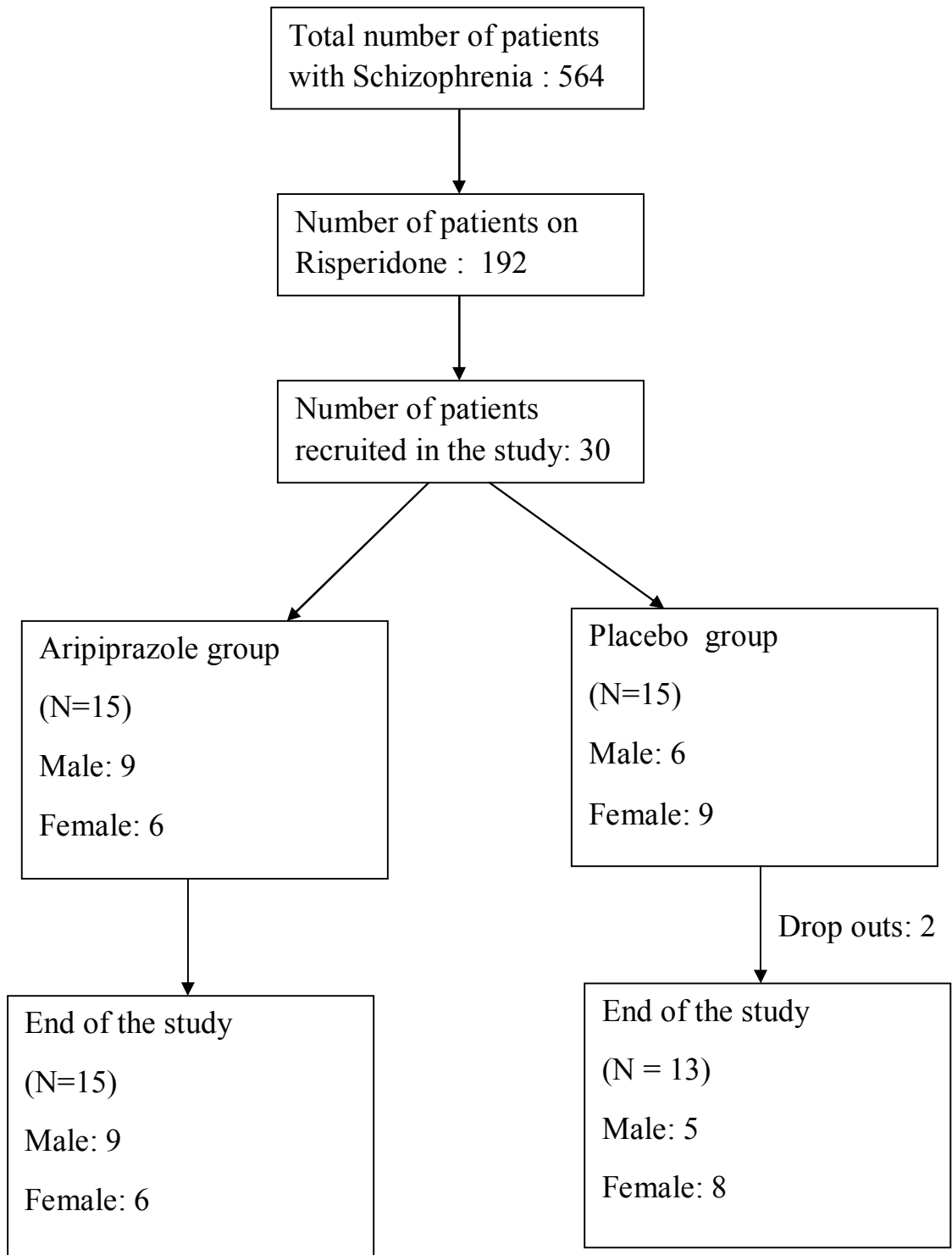
We compared the socio-demographic and clinical variables between Aripiprazole and placebo groups using student 't' and chi-square tests. Student't' test was used to assess the differences in the mean prolactin levels and chi-square test was used to assess the proportion of patients with hyperprolactinemia in both the groups. We used repeat measures analysis of variance (ANOVA) to evaluate the effect of time and the time-by-group interaction for prolactin levels, BPRS score (clinical rating scale), SAPS score, SANS score and Simson- Angus rating score. We considered an alpha level of <0.05 as statistically significant.

RESULTS



RESULTS

Fig: 6: Flowchart showing recruitment process



We reviewed our medical records and found that, between 1st January 2010 and 31st December 2010, 564 patients with the diagnosis of schizophrenia were attending our outpatient clinics. Among them 192 patients were on Risperidone. We recruited consecutive 30 patients who met our intake criteria. (Fig 6)

DROP OUTS

Two patients from the placebo group dropped out and none from the aripiprazole group. First patient dropped out due to difficulties in attending follow up visits once in every 2 weeks. Second patient was dropped out from the study due to worsening of clinical picture. She developed insomnia, loss of appetite and worsening of behavioral problems.

Socio- demographic profile

We had 9 males and 6 females in the Aripiprazole group and 6 males and 9 females in the placebo group and the mean age of the whole group was 32.33 (SD=8.29) and there was no difference in the ages and gender between the groups. (Table 1)

Table 1 - Mean age

	Male n=15	Female n=15
Aripiprazole group	33.67	30.50
Placebo group	31.17	30.67

p= 0.92

Except one patient, all are literates and majority of them (50%) have educated between 6th class to 12th class. (Table: 2)

Table: 2 Educational qualifications.

Education.	Frequency N	Percentage
Illiterate	1	3.3%
Up to V std.	3	10%
VI std to XII std.	15	50%
Diploma/ Under graduates	7	23.3%
Post graduates/ Professional courses.	4	13.3%

50% of them were married. (Table: 3)

Table: 3- Marital status.

	Married n= 15 (%)	Unmarried n= 15(%)
Aripiprazole group	10 (66.7)	5 (33.3)
Placebo group	5 (33.3)	10 (66.7)

p= 0.07

There is no difference between the aripiprazole group and placebo group in marital status and educational status.

The dose of Risperidone ranged between 4 mg to 10 mg. (Table: 4)

Table: 4 – Risperidone dose.

Variable.	Mean Risperidone dose mg	SD
Total group	6	1.174
Aripiprazole group	6.27	1.49
Placebo group	5.73	0.70

p Value- 0.22

SD- Standard deviation.

Prolactin level

Baseline Serum Prolactin Level

The mean prolactin level in the whole group was 1760.23 IU/L and there is no statistical difference between the Aripiprazole and placebo groups. The prolactin levels in females was consistently higher than males ($p < 0.001$); however there is no statistical difference among the respective gender in the Aripiprazole and placebo groups. (Table: 5)

Table: 5- Baseline Serum Prolactin Level

	Total Mean	Aripiprazole Mean (SD)	Placebo Mean (SD)	P value.
Total	1760.23	1,408 (1336)	2,112 (1,648.3)	0.209
Male	706.87	590.56 (256.82)	881.33 (297.77)	0.07
Female	2813.60	2,634.17 (1373.5)	2933.22 (1674.67)	0.723

Prolactin level:

At the end of 8 weeks, prolactin level in the Aripiprazole group had reduced significantly compared to placebo group, demonstrating a significant **time effect**, ($f = 6.33$, $df = 1, 26$, $p = 0.018$) and **time by group interaction** ($f = 5.512$, $df = 1, 26$, $p = 0.032$) on repeated measures ANOVA. No significant effect was observed in the placebo group on time.

Table: 6 shows difference in prolactin level between the two study groups at the end of 8 weeks and it is statistically significant.

Table: 6- Difference in Serum Prolactin level- At the end of 8 weeks.

	Aripiprazole Mean (SD)	Placebo Mean (SD)	P value.
End of 8 weeks	554.27 (558.9)	2,170 (1405.22)	<0.001*

*- $t = -4.105$, $df (26)$, $CI = 95\%$, (-2425.5 to -806.89)

Univariate analysis (Student's t test) also show that there is a significant reduction in prolactin level in the Aripiprazole group when compared to placebo group. (Table: 7).

Table: 7-Mean Reduction in Prolactin level- Aripiprazole and placebo groups

	Baseline Mean (SD)	End of 8 weeks Mean (SD)	t- Value	p- Value
Aripiprazole Group	1408 (1336)	554.27 (558.9)	3.727, $df (14)$	0.002*
Placebo Group	2,214.31 (1.745.23)	2170.46 (1,405.22)	-	0.877

Gender differences in prolactin level

At the baseline, mean prolactin levels for females (2812.60) was much higher than males (707.87), which was statistically significant (p value < 0.001). However, as we had done gender based stratified randomization, mean prolactin levels in males were comparable between Aripiprazole and placebo groups and similarly mean prolactin levels in females were comparable between both the groups. Table: 8.

Table: 8- Gender Differences in Prolactin level - Baseline

Gender	Aripiprazole Mean (SD)	Placebo Mean (SD)	p- Value.
Male.	590. 56 (256.82)	881.33 (297.77)	0.07
Female	2,634.17 (1373.5)	2933.22 (1674.67)	0.723

At the end of 8 weeks, there is statistically significant difference in prolactin levels between Aripiprazole group and placebo group in both the gender. (Table: 9)

Table: 9- Gender difference in Prolactin level- End of 8 weeks

Gender	Aripiprazole Mean (SD)	Placebo Mean (SD)	p- Value.
Male.	218.33 (131.99)	1097.40 (272.63)	< 0.001*
Female	1058.17 (582.28)	2841.12 (1416.37)	0.014*

* - Statistically significant.

Hyperprolactinemia

At the base line 86.7% of male patients and all the female patients have hyperprolactinemia. At the end of 8 weeks, only 22.2% of male patients had hyperprolactinemia but there was no change in the female group. (Table: 10 & 11)

Table: 10- Hyperprolactinemia- Male

Male	Aripiprazole (N= 9)		Placebo (N = 6)	
	HP	Normal	HP	Normal
Base line	7 (77.8%)	2 (22.2%)	6 (100%)	0
End of 8weeks	2 (22.2%)	7 (77.8%)	6 (100%)	0

HP:Hyperprolactinemia

Table: 11- Hyperprolactinemia- Female.

Female.	Aripiprazole (N= 6)		Placebo (N = 9)	
	HP.	Normal.	HP.	Normal.
Base line	6 (100%)	0	9 (100%)	0
End of the study.	6 (100%)	0	7 (100%)	0

Prolactin related physical symptoms

Findings of Arizona Sexual Experience Scale (ASEX) and Prolactin Related Adverse Events Questionnaire. (PRAEQ)

There is no statistically significant difference between the scores at the baseline.

Table: 12- Baseline difference between groups.

	Mean	SD	Aripiprazole	Placebo	P
ASEX	13.8	2.91	13.27(3.01)	14.33(2.82)	0.32
PRAEQ	28.27	12.28	29.60(13.60)	26.93(11.11)	0.56

At the end of 8 weeks there is significant difference in the ASEX total score but this difference was not noted in PRAEQ.

Table 13- End of 8 weeks

	Mean	SD	Aripiprazole	Placebo	P
ASEX	12.86	3.027	11.73(2.99)	14.15(2.609)	0.032*
PRAEQ	23.86	11.6	22.07(12.00)	25.92(11.37)	0.393

*- Statistically significant.

In Aripiprazole group, there is statistically significant difference between the mean scores at the baseline and the end of the study, which means patients in the Aripiprazole group had improvement in their menstrual and sexual functions. (Table: 14)

Table: 14- Reduction from the baseline- Aripiprazole group

	Mean difference.	t- value	p- value
PRAEQ	- 7.533	-4.923	<0.001*+
ASEX	-1.533	-2.78	0.015*

However this difference is not noted in the placebo group as shown in the Table: 15

Table: 15- Reduction from the baseline- Placebo group

	Mean difference	t- value	p- value
PRAEQ	+0.231	+0.359	0.726
ASEX	_0.077	_0.158	0.877

Psychopathology ratings

Baseline

The mean BPRS and SAPS scores were less (9.3 and 4.23) indicating that our subjects had very minimal positive symptoms, on the other hand they had significant negative symptoms as scored by SANS. Their extra pyramidal symptoms were minimal as scored by SAES and none of them had any sign of akathisia.

(Table: 16) There is no statically significant difference between two study groups in BPRS, SAPS, BARNES and SAES as indicated by their p values.

Table: 16- Baseline clinical variables- Difference between study groups.

	Total Mean	SD	Aripiprazole group. Mean(SD)	Placebo group. Mean(SD)	P Value
SAPS	4.23	6.36	5.2(6.92)	3.27(5.82)	0.41
SANS	25.7	12.14	22.53(10.81)	28.87	0.16
BPRS	9.3	5.49	9.6(5.81)	9.00(5.33)	0.77
BARNES	0	0	0	0	
SAES	3.5	1.75	3.27(2.052))	3.73(1.438)	0.48

We did not find any difference between the aripiprazole group and the placebo group at the end of 8 weeks. (Table: 17).

Table: 17- Difference between the study groups at the end of 8 Weeks.

	Total Mean	SD	Aripiprazole group. Mean(SD)	Placebo group. Mean(SD)	Mean difference	P value
SAPS	4.39	7.026	6.6(8.65)	1.85(3.24)	4.754	0.073
SANS	23.68	9.109	20.67(9.40)	27.15(7.69)	6.487	0.059
BPRS	8.43	4.36	9.53(5.31)	7.15(2.54)	2.38	0.153
BARNES	0	0	0	0	0	
SAES	3.29	1.58	3.00(1.732)	3.62(1.39)	0.615	0.599

$$a- t = - 2.267, df (26)$$

SAPS- Scale for Assessment of Positive Symptoms; SANS- Scale for Assessment of Negative Symptoms; BPRS- Brief Psychiatric Rating Scale; BARNES- Barnes Akathisia Rating Scale; SAES- Simpson Angus Extra Pyramidal Symptoms Scale.

Table: 18- Difference from the base line at the end of the study for Psychopathology variables

	Aripiprazole group		Placebo group	
	Mean difference (SD)	P value	Mean difference (SD)	P value
SAPS	+ 1.4 (5.74)	0.361	_ 0.462 (0.97)	0.111
SANS	_ 1.86(5.902)	0.241	_ 1.538(3.99)	0.19
BPRS	_0.067	0.961	_0.615	0.321
BARNES	0		0	
SAES	_0.267	0.104	_0.077	0.721

There is no statistically significant difference in clinical variables at the end of study from the base line in either group. (Table: 18)

Adverse effects

1. Two patients from the Aripiprazole group reported worsening of psychotic symptoms after 2 weeks but they were clinically stable and were treated with Lorazepam.
2. Two patients in the Aripiprazole group developed symptoms suggestive of gastritis and was treated with proton pump blockers.
3. One patient in the Aripiprazole group developed galactocoele, which was secondary to a traumatic injury, as evaluated by our surgery department.
4. One patient in the placebo group developed insomnia which was transient and responded to short course of Benzodiazepines.
5. One patient from placebo group developed fever with hepatitis during the last week of follow up and was diagnosed as infectious hepatitis.

DISCUSSION



DISCUSSION

We studied adjunctive treatment with Aripiprazole for hyperprolactinemia induced by Risperidone and we conclude that there was a very significant reduction in prolactin levels over the 8 weeks in both males and females. They also had improvement in sexual functions. These benefits occurred without any change in their psychopathology and without any adverse effects.

Among neuroleptics, risperidone causes maximum raise in prolactin levels (21), but still there are only few studies addressing this issue. As we could not locate any publication similar to our study, we believe that this is the first randomized controlled study in studying the effects of adding aripiprazole to risperidone induced hyperprolactinemia.

We used reduction in prolactin level from the baseline as the primary outcome. Whether this reduction in prolactin levels would lead to clinically meaningful improvement in sexual side effects was evaluated with Arizona sexual experience scale and Prolactin Related Adverse Event questionnaire. Arizona sexual experience scale is a valid and reliable tool that is widely used for measuring sexual dysfunctions (47) but Prolactin Related adverse Event Questionnaire needs further validation. However it gives objective measurement of side effects related to hyperprolactinemia and it was very easy to administer and covers wide range of symptom profile.

Prolactin Level

At the end of our study there is reduction in prolactin level in Aripiprazole group compared to placebo group which is statistically significant ($p < 0.001$). **There is 60.6% reduction in prolactin level from the baseline in Aripiprazole group.**

This percentage change is noted in both the sexes at the end of 8 weeks which is similar to findings replicated in another study (24).

In our sample, Risperidone had caused greater prolactin elevations in female patients than male patients, which was statistically significant. We found 86.7% men and 100% women treated with Risperidone had hyperprolactinemia at the baseline and this findings support existing literature that Risperidone causes hyperprolactinemia in 90% of the patients. (22, 24)

At the end of 8 weeks, 77.8% male patients in Aripiprazole group became normal and none of the male patients in the placebo group normalized. (Pearson chi square value is 8.750 with $p = 0.003$ which is statistically significant.)

However none of female patients in Aripiprazole and placebo group normalized at the end of the study even though there is statistically and clinically significant reduction in Aripiprazole group.

We hypothesize that the dose of Aripiprazole (10 mg) may not be enough for complete normalization in all female patients and some of the male patients. Shim et al, 2007 (24) have used 15 mg and 30 mg of Aripiprazole given as adjuvant to Haloperidol to treat hyperprolactinemia.

But there is an open label trial (48) stating there is no significant reduction in serum prolactin level noted above 6 mg Aripiprazole. Adjunctive Aripiprazole was added to patients on risperidone and the Aripiprazole dose was gradually increased from 3 mg to 12 mg and serum prolactin was measured with each increase in the dose. It was found that reduction in prolactin level occurs with 3 mg of Aripiprazole and achieves a plateau at dosage beyond 6 mg.

In a randomized control Trial (49), Potkin et al compared Aripiprazole 20 mg with Aripiprazole 30 mg. It was found out that both the Aripiprazole group has significant reduction in serum prolactin level from the base line. In the 20 mg group, mean reduction was 54.5%. In 30 mg group, mean reduction was 50.4%. It was found that there is no statistically significant difference between 20 mg and 30 mg of Aripiprazole in terms of reduction in prolactin level.

It was also hypothesized that Aripiprazole if given for a longer duration in a low dose may normalize hyperprolactinemia. But this needs further research with frequent prolactin level measurement and different doses of Aripiprazole to confirm the hypothesis.

Prolactin related sexual side effects

92% of female patients have menstrual disturbances at the baseline but chest symptoms were present in only 40% of the female patients. None of the male patients have chest symptoms as it is well known that it is rare in male population. (50). Almost all the male patients have disturbances in penile functions including erectile and ejaculatory dysfunction.

In our study it was found that there is statistically significant reduction in mean Arizona sexual Experience Scale and Prolactin Related Adverse Events Questionnaire in Aripiprazole group at the end of 8 weeks but this difference was not noted in placebo group.

This is similar to the findings replicated in an open label, naturalistic, multicenter trial with a sample size of 555, where they compared Aripiprazole with other atypical antipsychotic agents (51). Authors have found out there is statistically significant improvement in mean Arizona Sexual Experience Scale in Aripiprazole group at the end of 26 weeks; However in our study there is improvement as early as 8 weeks.

In female patients, clinically significant improvement in chest symptoms was observed in Aripiprazole group but very minimal improvement was noted in menstrual disturbances.

In male patients there was clinically significant improvement in erectile dysfunction in Aripiprazole group.

There is no difference between the baseline demographic and clinical variables. Since we recruited patients who were maintaining well on Risperidone, our mean SAPS and BPRS scores were low (4.23 and 9.3). However our participants scored high on negative symptoms as indicated by mean SANS score (25.7)

Since almost all the patients were taking Trihexyphenidyl along with Risperidone, mean score of Simpson Angus Extra Pyramidal symptoms Rating Scale was only 3.5 and the subjects were allowed to continue the Trihexyphenidyl and none of them experienced extrapyramidal symptoms during the study. None of our patients had akathisia at the baseline and at the end of 8 weeks.

At the end of 8 weeks, we found no significant change in psychopathology between the groups. None of the subjects required hospital admission or dose modification of Risperidone for the worsening of symptoms.

However we should be cautious since there are case reports of worsening of positive symptoms due to treatment with Aripiprazole especially when it is added with other antipsychotics. (52) (53) (54)

There is reduction in mean SANS score in Aripiprazole group from the baseline but it was not statistically significant. This finding is similar to another study, where there is reduction in negative symptoms with adjunctive Aripiprazole treatment yet there is no statistically significant reduction (24).

The subjects in our study were chronically ill and clinically stable patients. These characteristics of our study subjects may make it difficult to find further improvements in negative symptoms, especially in only 8 weeks. However formal study is warranted to study the role of Aripiprazole in treating negative symptoms as it is theoretically possible.

LIMITATIONS



LIMITATIONS

1. We calculated sample size only for the primary outcome but for sub group analysis our sample size may not be enough.
2. Arizona Sexual Experience Scale and Prolactin Related Adverse Event Questionnaire are not validated for our Indian setting.
3. Drug levels are not measured.
4. Compliance to Risperidone as well as the study drugs were assumed; however to reduce non-compliance we followed them every two weeks and gave study drugs.

CONCLUSION



CONCLUSION

From our study, we conclude that with 8 weeks of adjunctive treatment of Aripiprazole in patients with Risperidone induced hyperprolactinemia, there are significant reductions in prolactin levels and even leads to normalization of hyperprolactinemia in some patients.

There is clinical improvement in sexual side effects along with biochemical improvement.

This method is safe and well tolerated and highly beneficial to individuals suffering from adverse effects because of hyperprolactinemia.

However further studies are required to find out the optimal dose of Aripiprazole and duration to achieve the desired outcome. Further studies are required to find out the effects of Aripiprazole in psychopathology especially improvement in negative symptoms.

REFERENCES



REFERENCES

1. Liberman JA et al. Catching Up on Schizophrenia: Review
Natural History and Neurobiology. *Neuron*. 2000 Nov; 28: 325-34.
2. World Health Organization [online]. Available from: URL:
http://www.who.int/mental_health/management/schizophrenia/en/
3. Kane JM. Drug therapy Schizophrenia. *N Engl J Med*. 1996; 334:
34-41
4. Geddes J et al. Atypical antipsychotics in the treatment of
schizophrenia: systematic overview and meta-regression analysis.
BMJ. 2000 Dec 2; 321: 1371-6.
5. Lieberman JA et al. Effectiveness of Antipsychotic Drugs in Patients
with Chronic Schizophrenia (CATIE). *N Engl J Med*. 2005 Sep 22;
353: 1209-23.
6. John M et al. A Meta-analysis of the Efficacy of Second- Generation
Antipsychotics. *Arch Gen Psychiatry*. 2003; 60: 553- 64.
7. Lehman FA et al. The Schizophrenia Patient Outcomes Research
Team (PORT): Updated Treatment Recommendations 2003.
Schizophr bul. 2004; 30(2): 193- 217.

8. Chouinard G et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol*.1993 Feb; 13(1):25- 40.
9. Manschreck TC, Boshes RA. The CATIE schizophrenia trial: results, impact, controversy. *Harv Rev Psychiatry*. 2007 Sep- Oct; 15(5): p245- 58.
10. Conley RR, Mahmoud R. A Randomized Double-Blind Study of Risperidone and Olanzapine in the Treatment of Schizophrenia or Schizoaffective Disorder. *Am J Psychiatry*. 2001; 158:765–774.
11. Conley RR. Risperidone side effects. *J Clin Psychiatry*. 2000; 61 Suppl. 8:20-3; discussion 24-5.
12. Freeman Me, Kanyicska B, Lerant A, Nagy G. Prolactin: Structure, function and regulation of secretion. *Physiol Rev*. 2000; 80(4): 1523-1621.
13. Goffin V, Binart N, Touraine P, Kelly PA. Prolactin: the new biology of an old hormone. *Annu Rev Physiol*. 2002; 64: 47- 67.

14. Perkins DO. Antipsychotics induced hyperprolactinemia: Pathophysiology and clinical consequences. *Adv Stud Med.* 2004; 4(10F): S982- 6.
15. Kristina Melkersson. Differences in Prolactin Elevation and Related Symptoms of Atypical Antipsychotics in Schizophrenic Patients. *Clin Psychiatry.* 2005;66(6):761-7.
16. Jan Volavka. Prolactin Levels in Schizophrenia and Schizoaffective Disorder Patients Treated With Clozapine, Olanzapine, Risperidone, or Haloperidol. *J Clin Psychiatry.* 2004;65:p57-61.
17. Bruce J Kinon, Julie A Gilmore, Hong Liu, Uriel M. Prevalence of Hyper prolactinemia in schizophrenic patients treated with conventional antipsychotic medications or Risperidone. *Psychoneuroendocrinology.* 2003 Apr;28 (Suppl 2):55-68.
18. Meany A et al. Hyperprolactinemia and osteoporosis in schizophrenia. *Br J Psychiatry.* 2004; 184: 503- 8.
19. Wang PS, Walker AM, Tsuang MT et al. Dopamine agonists and the development of breast cancer. *Arch Gen Psychiatry.* 2002; 59(12): 1147- 54.

20. Cutler AJ. Sexual dysfunction and antipsychotic treatment. *Psychoneuroendocrinology*. 2003; 28(suppl 1): 69- 82.
21. David SR, Taylor CC, Kinon BJ, Breier A. The effects of olanzapine, risperidone and haloperidol on plasma prolactin levels in patients with schizophrenia. *Clin Ther*. 2000; 22(9): 1085- 96.
22. Wyszogrodzka-kucharska et al. Prolactin secretion disturbances in schizophrenic patients treated with 2nd generation antipsychotics- risperidone and olanzapine. *Psychiatr Pol*. 2005 Nov-Dec;39(6):p1143-55.
23. Kapur S, Langlois X, Vinken P, Megens AA, Coster R, Andrews JS. The differential effects of antipsychotics on prolactin elevation are explained by their differential blood-brain disposition: a pharmacological analysis in rats. *J Pharmacol Exp Ther*. 2002; 302(3): 1129-34.
24. Joo-cheol shim et al. Adjunctive treatment with a dopamine partial agonist Aripiprazole ,for antipsychotic-induced hyperprolactinemia: A Placebo controlled trial. *Am j psychiatry*. 2007 sep;164(9):p1404-10.
25. Lieberman JA. Dopamine partial agonists: a new class of antipsychotic. *CNS Drugs*. 2004;18(4):251-67.

26. Cada Dj, Levien, T, Baker DE. Aripiprazole. *Hospital pharmacy* 2003;38:p247-256.
27. Lee HY et al. Trial of aripiprazole in the treatment of first-episode schizophrenia. *Psychiatry Clin Neurosci*. 2010 Feb;64(1):p38-43.
28. Amna Mir et al. Change in sexual dysfunction with aripiprazole: a switching or add-on study. *Journal of Psychopharmacology*. 2008 May 1;22(3):p244-53.
29. Martin baggaley. Review of sexual dysfunction: Focus on recent evidence. *Human psychopharmacology*. 2008 Mar 13;23(3):p201-9
30. Vieta e et al. Effect of aripiprazole vs. haloperidol in acute bipolar mania: Double blind, randomized, comparative 12 week trial. *Br J Psychiatry*. 2005;187:235-42.
31. Chan HY et al. Efficacy and safety of aripiprazole in acute management of Schizophrenia in Chinese patients with risperidone as a active control. A randomized trial. *J Clin Psychiatry*. 2007; 68:29-36.

32. Lee BH, Kim YK, Park SH. Using Aripiprazole for resolving antipsychotics induced symptomatic hyperprolactinemia. A pilot study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006; 30:p 714-7.
33. Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry*. 2002; 63:763–771
34. Keck PE Jr, Marcus R, Tourkodimitris S, et al. A placebocontrolled, double-blind study of the efficacy and safety of Aripiprazole in patients with acute bipolar mania. *Am J Psychiatry*. 2003; 160:1651–8.
35. Steven G et al. Aripiprazole, an Antipsychotic With a Novel Mechanism of Action, and Risperidone vs. Placebo in Patients With Schizophrenia and Schizoaffective Disorder. *Arch Gen Psychiatry*. 2003;60:681-90.
36. Zachary SH et al. Evidence for partial dopamine receptor agonists Aripiprazole as a first-line treatment of Psychosis with Iatrogenic or Tumourogenic hyperprolactinemia. *Psychosomatics*. 2009 jul/aug ; 50(4):p 317.

- 37.Marder SR, McQuade RD, Stock E, et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. *Schizophr Res*. 2003; 61:123–36.
- 38.Lorenz RA, Weinstein B. Resolution of haloperidol-induced hyperprolactinemia with aripiprazole. *J Clin Psychopharmacol*. 2007; 27:524 – 5.
- 39.Jing xu chen MD et al. Aripiprazole treatment of risperidone induced hyperprolactinemia. *J clin psychiatry*. 2009 Jul;70(7):p1058-9.
- 40.Rebecca W, Robert O. Reversal of symptomatic hyper prolactinemia by Aripiprazole. *Am J Psychiatry*. Aug 2005;162(8):p1542.
- 41.Wahl R, Ostroff R. Reversal of symptomatic hyperprolactinemiaby aripiprazole. *Am J Psychiatry*. 2005; 162:1542–1543
- 42.Hedlund JL, Vieweg BW. The Brief Psychiatric Rating Scale (BPRS): a comprehensive review. *Journal of Operational Psychology*. 1980; 11:48-62.
- 43.Overall JE, Gorham DR. The Brief Psychiatric Rating Scale (BPRS):A Comprehensive review. *J Oper Psychiatry*. 1991; 148:p472.

44. Andreasen NC, Arndt S, Miller D, Flaum M, Nopoulos P. Correlational studies of the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms: An overview and update. *Psychopathology*. 1995;28:7.
45. Thomas R E Barnes. Rating scale for drug induced akathisia. *Br J Psychiatry*. 1989; 154:p 672-6.
46. Simpson GM, Angus JWS. A rating scale for extra pyramidal side effects. *Acta Psychiatr Scand*. 1970;46(suppl 212):11.
47. McGahuey et al. The Arizona Sexual Experience Scale(ASEX): Reliability and Validity. *J sex Marital Ther*. 2000 jan-mar;26(1):p 25-40.
48. Furukori YN, Furukori H, Sugawara N, Fujii A, Kaneko S. Dose-dependent effects of adjunctive treatment with aripiprazole on hyperprolactinemia induced by risperidone in female patients with schizophrenia. *J Clin Psychopharmacol*. 2010 Oct;30(5):596-9
49. Potkin SG, Saha AR, Kujawa MJ, et al. Aripiprazole: an antipsychotic with a novel mechanism of action, and risperidone vs. placebo in patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry*. 2003; 60:681–90.

50. Schlechte JA: Prolactinoma. *N Engl J Med*. 2003; 349:2035–41.
51. Linda H et al. The effect of antipsychotic medication on sexual function and serum prolactin levels in community-treated schizophrenic patients: results from the Schizophrenia Trial of Aripiprazole (STAR) study (NCT00237913). *BMC Psychiatry*. 2008. 8;95.
52. Barnas ME, Hussain N, Petrides G. Treatment- emergent psychosis with Aripiprazole [letter]. *J Clin Psychiatry*. 2005; 66: 1339.
53. Reeves RR, Mack JE. Worsening of schizoaffective disorder with Aripiprazole [letter]. *Am J Psychiatry*. 2004; 161: 1308.
54. Ramaswamy et al. Aripiprazole possibly worsens psychosis. *Int Clin Psychopharmacol*. 2004 Jan; 19(1): 45-8.

APPENDIX - I



Supplementation of Aripiprazole in Risperidone induced hyperprolactinemia: A double blind Randomized placebo controlled trial.

Date:

OP NO:

Name:

Age:

Sex:

Marital status : Married / Single / Separate/divorced

Monthly Income:

Education :

Employment :

Diagnosis:

Events: Prolactin level at the beginning of study

Prolactin level at the end of 8 weeks

Adverse events during past 2 weeks:

2ND WEEK	
4TH WEEK	
6TH WEEK	
8TH WEEK	

Assessed by:

APPENDIX -II



INFORMED CONSENT

Title of the study: A Double Blind Randomized Placebo controlled trial: Augmentation of Aripiprazole for Risperidone induced hyper prolactinemia..

Information to the participants: You are diagnosed to have schizophrenia maintaining on Risperidone. This medication you are taking for schizophrenia has the complication of hyper prolactinemia. There is possibility of long term side effects due to Risperidone induced hyper prolactinemia like decrease in bone mineral density and immediate complications like menstrual abnormality, sexual dysfunction according to available literature. Switching to other antipsychotic, there is possibility of relapse of symptoms of schizophrenia. So with available literature augmentation with Aripiprazole causes reduction in hyper prolactinemia and its complications. The Side effects of Aripiprazole are akathisia , hypersensitivity, insomnia which can be managed symptomatically and we are regularly monitoring for side effects during follow up. You will be randomly assigned to either Aripiprazole/placebo after base line prolactin assessment for which 3ml of blood sample will be taken. Neither you nor the primary investigators will know that to which group you actually belong to. You will be given Aripiprazole/placebo totally for 8 weeks. Follow up will be there every 2 weeks to objectively assess any side effects, improvement in symptoms and to collect the drugs for next 2 weeks. At the end of the study prolactin level is done again after collecting 3 ml of blood.

Undertaking by the Investigator: Your consent to participate in the study is sought. You have the right to refuse consent or withdraw the same during any part of the study without giving any reason. In such instance you will still receive the best possible treatment, without any prejudice. If you have any doubts about the study, please feel free to clarify the same (phone numbers and contact addresses will be provided to you) at any time. All your records will be kept strictly confidential.

Thesis student: Dr.R.Venkateswaran, ph- 9994474538

Thesis guide: Dr.Raghuthaman.

Consent: I have been informed about the procedures of the study. The possible risks too have been explained to me as stated above. I have understood that I have the right to refuse my consent or withdraw it any time during the study without adversely affecting my/my ward's treatment. I have been provided ample time to ask questions and I Have been clarified to my satisfaction. I am also aware that by subjecting myself to this study, I will have to give more time for assessments by the doctor and that these assessments do not interfere with the benefits.

I,, the undersigned, give my consent to be a participant of this study.

SIGNATURE OF THE PATIENT/GUARDIAN:

NAME:

ADDRESS AND PHONE NUMBER:

SIGNATURE OF WITNESS:

NAME:

SIGNATURE OF THE DOCTOR:

NAME:

DESIGNATION:

DATE:

PLACE:

In case of Illiterates: I have been explained the contents of the informed consent in a language understandable to me and I am signing this document on my own.

THUMB IMPRESSION

OF THE PATIENT:

NAME:

THUMB IMPRESSION

OF THE WITNESS:

NAME:

APPENDIX - III



SCALE FOR THE ASSESSMENT OF POSITIVE SYMPTOMS

(SAPS)

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(SAS Variable Name edition: 2000)

INTRODUCTION

This scale is designed to assess positive symptoms, principally those that occur in schizophrenia. It is intended to serve as a complementary instrument to the Scale for the Assessment of Negative Symptoms (SANS). These positive symptoms include hallucinations, delusions, bizarre behavior, and positive formal thought disorder.

As in the case of the SANS, the investigator using this instrument will need to decide on an appropriate "time set". The instrument was developed with the exception that, in general, the time set will cover the past month as in the case of SANS. This scale can also be used in psychopharmacologic research in order to make weekly ratings and chart the subject's response to treatment.

Investigators using this instrument, particularly in combination with the SANS, will need to use a standard clinical interview in order to evaluate the subject's symptoms. Since positive formal thought disorder is an important positive symptom, it is recommended that, in doing this interview, the investigator begin talking with the subject on a relatively neutral topic for five to ten minutes in order to observe the subject's manner of speaking and responding. Thereafter, he can begin to ask specific questions about the various positive symptoms. Suggested probes are provided in the interview guide.

In addition to using a clinical interview, the investigator should also draw on other sources of information, such as direct observation, reports from the subject's family, reports from nurses, and reports from the subject himself. In general, the subject can usually be considered a relatively reliable informant concerning delusions and hallucinations if he is able to communicate clearly and will comply with a clinical interview. On the other hand, the interviewer will usually have to rely on observation and reports from outside sources in order to evaluate bizarre behavior and positive formal thought disorder.

The last item describing each major type of positive symptom is an overall global rating. This should be a true global rating based on taking into account both the nature and the severity of the various types of symptoms observed. In some cases, a single symptom (e.g., extremely severe persecutory delusions) may lead to a very high global rating, even if other symptoms of this type are not present.

HALLUCINATIONS

Hallucinations represent an abnormality in perception. They are false perceptions occurring in the absence of some identifiable external stimulus. They may be experienced in any of the sensory modalities, including hearing, touch, taste, smell, and vision. True hallucinations should be distinguished from illusions (which involve a misperception of an external stimulus), hypnogogic and hypnopompic experiences (which occur when the subject is falling asleep or waking up), or normal thought processes that are exceptionally vivid. If the hallucinations have a religious quality, then they should be judged within the context of what is normal for the subject's social and cultural background. Hallucinations occurring under the immediate influence of alcohol, drugs, or serious physical illness should not be rated as present. The subject should always be requested to describe the hallucination in detail.

Auditory Hallucinations

The subject has reported voices, noises, or sounds. The commonest auditory hallucinations involve hearing voices speaking to the subject or calling him names. The voices may be male or female, familiar or unfamiliar, and critical or complimentary. Typically, subjects suffering from schizophrenia experience the voices as unpleasant and negative. Hallucinations involving sounds rather than voices, such as noises or music, should be considered less characteristic and less severe.

Have you ever heard voices or other sounds when no one is around?

What did they say?

None	0	SS36
Questionable	1	
Mild: Subject hears noises or single words; they occur only occasionally	2	
Moderate: Clear evidence of voices; they have occurred at least weekly	3	
Marked: Clear evidence of voices which occur almost every day	4	
Severe: Voices occur often every day	5	

Voices Commenting

Voices commenting are a particular type of auditory hallucination which phenomenologists as Kurt Schneider consider to be pathognomonic of schizophrenia, although some recent evidence contradicts this. These hallucinations involve hearing a voice that makes a running commentary on the subject's behavior or thought as it occurs. If this is the only type of auditory hallucination that the subject hears, it should be scored instead of auditory hallucinations (No. 1 above). Usually, however, voices commenting will occur in addition to other types of auditory hallucinations.

Have you ever heard voices commenting on what you are thinking or doing?

What do they say?

None	0	SS37
Questionable	1	
Mild: Subject hears noises or single words; they occur only occasionally	2	
Moderate: Clear evidence of voices; they have occurred at least weekly	3	
Marked: Clear evidence of voices which occur almost every day	4	
Severe: Voices occur often every day	5	

Voices Conversing

Like voices commenting, voices conversing are considered a Schneiderian first-rank symptom. They involve hearing two or more voices talking with one another, usually discussing something about the subject. As in the case of voices commenting, they should be scored independently of other auditory hallucinations.

Have you heard two or more voices talking with each other?

What did they say?

None	0	SS38
Questionable	1	
Mild: Subject hears noises or single words; they occur only occasionally	2	
Moderate: Clear evidence of voices; they have occurred at least weekly	3	
Marked: Clear evidence of voices which occur almost every day	4	
Severe: Voices occur often every day	5	

Somatic or Tactile Hallucinations

These hallucinations involve experiencing peculiar physical sensations in the body. They include burning sensations, tingling, and perceptions that the body has changed in shape or size.

Have you ever had burning sensations or other strange feelings in your body?

What were they?

Did your body ever appear to change in shape or size?

None	0	SS39
Questionable	1	
Mild: Subject experiences peculiar physical sensations; they occur only occasionally	2	
Moderate: Clear evidence of somatic or tactile hallucinations; they have occurred at least weekly	3	
Marked: Clear evidence of somatic or tactile hallucinations which occur almost every day	4	
Severe: Hallucinations occur often every day	5	

Olfactory Hallucinations

The subject experiences unusual smells which are typically quite unpleasant. Sometimes the subject may believe that he himself smells. This belief should be scored here if the subject can actually smell the odor himself, but should be scored among delusions if he only believes that others can smell the odor.

Have you ever experienced any unusual smells or smells that others do not notice?

What were they?

None	0	SS40
Questionable	1	
Mild: Subject experiences unusual smells; they occur only occasionally	2	
Moderate: Clear evidence of olfactory hallucinations; they have occurred at least weekly	3	
Marked: Clear evidence of olfactory hallucinations; they occur almost every day	4	
Severe: Olfactory hallucinations occur often every day	5	

Visual Hallucinations

The subject sees shapes or people that are not actually present. Sometimes these are shapes or colors, but most typically they are figures of people or human-like objects. They may also be characters of a religious nature, such as the Devil or Christ. As always, visual hallucinations involving religious themes should be judged within the context of the subject's cultural background. Hypnogogic and hypnopompic visual hallucinations (which are relatively common) should be excluded, as should visual hallucinations occurring when the subject has been taking hallucinogenic drugs.

Have you had visions or seen things that other people cannot?

What did you see?

Did this occur when you were falling asleep or waking up?

Global Rating of Severity of Hallucinations

This global rating should be based on the duration and severity of hallucinations, the extent of the subject's preoccupation with the hallucinations, his degree of conviction, and their effect on his actions. Also consider the extent to which the hallucinations might be considered bizarre or unusual. Hallucinations not mentioned above, such as those involving taste, should be included in this rating.

None	0	SS41
Questionable	1	
Mild: Subject experiences visual hallucinations; they occur only occasionally	2	
Moderate: Clear evidence of visual hallucinations; they have occurred at least weekly	3	
Marked: Clear evidence of visual hallucinations which occur almost every day	4	
Severe: Hallucinations occur often every day	5	
None	0	SS42
Questionable	1	
Mild: Hallucinations definitely present, but occur infrequently; at times the subject may question their existence	2	
Moderate: Hallucinations are vivid and occur occasionally; they may bother him to some extent	3	
Marked: Hallucinations are quite vivid, occur frequently, and pervade his life	4	
Severe: Hallucinations occur almost daily and are sometimes unusual or bizarre; they are very vivid and extremely troubling	5	

DELUSIONS

Delusions represent an abnormality in content of thought. They are false beliefs that cannot be explained on the basis of the subject's cultural background. Although delusions are sometimes defined as "fixed false beliefs," in their mildest form delusions may persist only for weeks to months, and the subject may question his beliefs or doubt them. The subject's behavior may or may not be influenced by his delusions. The rating of severity of individual delusions and of the global severity of delusional thinking should take into account their persistence, their complexity, the extent to which the subject acts on them, the extent to which the subject doubts them, and the extent to which the beliefs deviate from those that normal people might have. For each positive rating, specific examples should be noted in the margin.

Persecutory Delusions

People suffering from persecutory delusions believe that they are being conspired against or persecuted in some way. Common manifestations include the belief that one is being followed, that one's mail is being opened, that one's room or office is bugged, that the telephone is tapped, or that police, government officials, neighbors, or fellow workers are harassing the subject. Persecutory delusions are sometimes relatively isolated or fragmented, but sometimes the subject has a complex set of delusions involving both a wide range of forms of persecution and a belief that there is a well-designed conspiracy behind them. For example, a subject may believe that his house is bugged and that he is being followed because the government wrongly considers him a secret agent for a foreign government; this delusion may be so complex that it explains almost everything that happens to him. The ratings of severity should be based on duration and complexity.

Have people been bothering you in any way?

Have you felt that people are against you?

Has anyone been trying to harm you in any way?

Has anyone been watching or monitoring you?

Delusions of Jealousy

The subject believes that his/her mate is having an affair with someone. Miscellaneous bits of information are construed as "evidence". The person usually goes to great effort to prove the existence of the affair, searching for hair in the bedclothes, the odor of shaving lotion or smoke on clothing, or receipts or checks indicating a gift has been bought for the lover. Elaborate plans are often made in order to trap the two together.

Have you ever worried that your husband (wife) might be unfaithful to you?

What evidence do you have?

None	0 SS43
Questionable	1
Mild: Delusional beliefs are simple and may be of several different types; subject may question them occasionally	2
Moderate: Clear, consistent delusion that is firmly held	3
Marked: Consistent, firmly-held delusion that the subject acts on	4
Severe: Complex well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre	5

None	0 SS44
Questionable	1
Mild: Delusion clearly present, but the subject may question it occasionally	2
Moderate: Clear consistent delusion that is firmly held	3
Marked: Consistent, firmly-held delusion that the subject acts on	4
Severe: Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre	5

Delusions of Sin or Guilt

The subject believes that he has committed some terrible sin or done something unforgivable. Sometimes the subject is excessively or inappropriately preoccupied with things he did wrong as a child, such as masturbating. Sometimes the subject feels responsible for causing some disastrous event, such as a fire or accident, with which he in fact has no connection. Sometimes these delusions may have a religious flavor, involving the belief that the sin is unpardonable and that the subject will suffer eternal punishment from God. Sometimes the subject simply believes that he deserves punishment by society. The subject may spend a good deal of time confessing these sins to whomever will listen.

Have you ever felt that you have done some terrible thing that you deserve to be punished for?

Grandiose Delusions

The subject believes that he has special powers or abilities. He may think he is actually some famous personage, such as a rock star, Napoleon, or Christ. He may believe he is writing some definitive book, composing a great piece of music, or developing some wonderful new invention. The subject is often suspicious that someone is trying to steal his ideas, and he may become quite irritable if his ideas are doubted.

Do you have any special or unusual abilities or talents?

Do you feel you are going to achieve great things?

None	0 SS45
Questionable	1
Mild: Delusional beliefs may be simple and may be of several different types; subject may question them occasionally	2
Moderate: Clear, consistent delusion that is firmly held	3
Marked: Consistent, firmly-held delusion that the subject acts on	4
Severe: Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre	5
None	0 SS46
Questionable	1
Mild: Delusional beliefs may be simple and may be of several different types; subject may question them occasionally	2
Moderate: Clear, consistent delusion that is firmly held	3
Marked: Consistent, firmly-held delusion that the subject acts on	4
Severe: Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre	5

Religious Delusions

The subject is preoccupied with false beliefs of a religious nature. Sometimes these exist within the context of a conventional religious system, such as beliefs about the Second Coming, the Antichrist, or possession by the Devil. At other times, they may involve an entirely new religious system or a pastiche of beliefs from a variety of religions, particularly Eastern religions, such as ideas about reincarnation or Nirvana. Religious delusions may be combined with grandiose delusions (if the subject considers himself a religious leader), delusions of guilt, or delusions of being controlled. Religious delusions must be outside the range considered normal for the subject's cultural and religious background.

Are you a religious person?

Have you had any unusual religious experiences?

What was your religious training as a child?

Somatic Delusions

The subject believes that somehow his body is diseased, abnormal, or changed. For example, he may believe that his stomach or brain is rotting, that his hands or penis have become enlarged, or that his facial features are unusual (dysmorphophobia). Sometimes somatic delusions are accompanied by tactile or other hallucinations, and when this occurs, both should be rated. (For example, the subject believes that he has ballbearings rolling around in his head, placed there by a dentist who filled his teeth, and can actually hear them clanking against one another.)

Is there anything wrong with your body?

Have you noticed any change in your appearance?

None	0 SS47
Questionable	1
Mild: Delusional beliefs may be simple and may be of several different types; subject may question them occasionally	2
Moderate: Clear, consistent delusion that is firmly held	3
Marked: Consistent, firmly-held delusion that the subject acts on	4
Severe: Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre	5
None	0 SS48
Questionable	1
Mild: Delusional beliefs may be simple and may be of several different types; subject may question them occasionally	2
Moderate: Clear, consistent delusion that is firmly held	3
Marked: Consistent, firmly-held delusion that the subject acts on	4
Severe: Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre	5

Ideas and Delusions of Reference

The subject believes that insignificant remarks, statements, or events refer to him or have some special meaning for him. For example, the subject walks into a room, sees people laughing, and suspects that they were just talking about him and laughing at him. Sometimes items read in the paper, heard on the radio, or seen on television are considered to be special messages to the subject. In the case of ideas of reference, the subject is suspicious, but recognizes his idea is erroneous. When the subject actually believes that the statements or events refer to him, then this is considered a delusion of reference.

Have you ever walked into a room and thought people were talking about you or laughing at you?

Have you seen things in magazines or on TV that seem to refer to you or contain a special message for you?

Have people communicated with you in any unusual ways?

Delusions of Being Controlled

The subject has a subjective experience that his feelings or actions are controlled by some outside force. The central requirement for this type of delusion is an actual strong subjective experience of being controlled. It does not include simple beliefs or ideas, such as that the subject is acting as an agent of God or that friends or parents are trying to coerce him to do something. Rather, the subject must describe, for example, that his body has been occupied by some alien force that is making it move in peculiar ways, or that messages are being sent to his brain by radio waves and causing him to experience particular feelings that he recognizes are not his own.

Have you ever felt you were being controlled by some outside force?

None	0	SS49
Questionable	1	
Mild: Occasional ideas of reference	2	
Moderate: Have occurred at least weekly	3	
Marked: Occurs at least two to four times weekly	4	
Severe: Occurs frequently	5	

None	0	SS50
Questionable	1	
Mild: Subject has experienced being controlled, but doubts it occasionally	2	
Moderate: Clear experience of control, which has occurred on two or three occasions in a week	3	
Marked: Clear experience of control, which occurs frequently; behavior may be affected	4	
Severe: Clear experience of control which occurs frequently, pervades the subject's life, and often affects his behavior	5	

Delusions of Mind Reading

The subject believes that people can read his mind or know his thoughts. This is different than thought broadcasting (see below) in that it is a belief without a percept. That is, the subject subjectively experiences and recognizes that others know his thoughts, but he does not think that they can be heard out loud.

Have you ever had the feeling that people could read your mind?

None	0	SS51
Questionable	1	
Mild: Subject has experienced mind reading, but doubts it occasionally	2	
Moderate: Clear experience of mind reading which has occurred on two or three occasions in a week	3	
Marked: Clear experience of mind reading which occurs frequently; behavior may be affected	4	
Severe: Clear experience of mind reading which occurs frequently, pervades the subject's life, and often affects his behavior	5	

Thought Broadcasting

The subject believes that his thoughts are broadcast so that he or others can hear them. Sometimes the subject experiences his thoughts as a voice outside his head; this is an auditory hallucination as well as a delusion. Sometimes the subject feels his thoughts are being broadcast although he cannot hear them himself. Sometimes he believes that his thoughts are picked up by a microphone and broadcast on the radio or television.

Have you ever heard your own thoughts out loud, as if they were a voice outside your head?

Have you ever felt your thoughts were broadcast so other people could hear them?

Thought Insertion

The subject believes that thoughts that are not his own have been inserted into his mind. For example, the subject may believe that a neighbor is practicing voodoo and planting alien sexual thoughts in his mind. This symptom should not be confused with experiencing unpleasant thoughts that the subject recognizes as his own, such as delusions of persecution or guilt.

Have you ever felt that thoughts were being put into your head by some outside force?

Have you ever experienced thoughts that didn't seem to be your own?

None	0 SS52
Questionable	1
Mild: Subject has experienced thought broadcasting, but doubts it occasionally	2
Moderate: Clear experience of thought broadcasting which has occurred on two or three occasions in a week	3
Marked: Clear experience of thought broadcasting which occurs frequently; behavior may be affected	4
Severe: Clear experience of thought broadcasting which occurs frequently, pervades the subject's life, and often affects his behavior	5
None	0 SS53
Questionable	1
Mild: Subject has experienced thought insertion, but doubts it occasionally	2
Moderate: Clear experience of thought insertion which has occurred on two or three occasions in a week	3
Marked: Clear experience of thought insertion which occurs frequently; behavior may be affected	4
Severe: Thought insertion which occurs frequently, pervades the subject's life and affects behavior	5

Thought Withdrawal

The subject believes that thoughts have been taken away from his mind. He is able to describe a subjective experience of beginning a thought and then suddenly having it removed by some outside force. This symptom does not include the mere subjective recognition of alogia.

Have you ever felt your thoughts were taken away by some outside force?

None	0 SS54
Questionable	1
Mild: Subject has experienced thought withdrawal, but doubts it occasionally	2
Moderate: Clear experience of thought withdrawal which has occurred on two or three occasions in a week	3
Marked: Clear experience of thought withdrawal which occurs frequently; behavior may be affected	4
Severe: Clear experience of thought withdrawal which occurs frequently, pervades the subject's life and often affects his behavior	5

Global Rating of Severity of Delusions

The global rating should be based on duration and persistence of delusions, the extent of the subject's preoccupation with the delusions, his degree of conviction, and their effect on his actions. Also consider the extent to which the delusions might be considered bizarre or unusual. Delusions not mentioned above should be included in this rating.

None	0 SS55
Questionable	1
Mild: Delusion definitely present but, at times, the subject questions the belief	2
Moderate: The subject is convinced of the belief, but it may occur infrequently and have little effect on his behavior	3
Marked: The delusion is firmly held; it occurs frequently and affects the subject's behavior	4
Severe: Delusions are complex, well-formed, and pervasive; they are firmly held and have a major effect on the subject's behavior; they may be somewhat bizarre or unusual	5

BIZARRE BEHAVIOR

The subject's behavior is unusual, bizarre, or fantastic. For example, the subject may urinate in a sugar bowl, paint the two halves of his body different colors, or kill a litter of pigs by smashing their heads against a wall. The information for this item will sometimes come from the subject, sometimes from other sources, and sometimes from direct observation. Bizarre behavior due to the immediate effects of alcohol or drugs should be excluded. As always, social and cultural norms must be considered in making the ratings, and detailed examples should be elicited and noted.

Clothing and Appearance

The subject dresses in an unusual manner or does other strange things to alter his appearance. For example, he may shave off all his hair or paint parts of his body different colors. His clothing may be quite unusual; for example, he may choose to wear some outfit that appears generally inappropriate and unacceptable, such as a baseball cap backwards with rubber galoshes and long underwear covered by denim overalls. He may dress in a fantastic costume representing some historical personage or a man from outer space. He may wear clothing completely inappropriate to the climatic conditions, such as heavy wools in the midst of summer.

Has anyone made comments about your appearance?

None	0 SS56
Questionable	1
Mild: Occasional oddities of dress or appearance	2
Moderate: Appearance or apparel are clearly unusual and would attract attention	3
Marked: Appearance or apparel are markedly odd	4
Severe: Subject's appearance or apparel are very fantastic or bizarre	5

Social and Sexual Behavior

The subject may do things that are considered inappropriate according to usual social norms. For example, he may masturbate in public, urinate or defecate in inappropriate receptacles, or exhibit his sex organs inappropriately. He may walk along the street muttering to himself, or he may begin talking to people whom he has never met about his personal life (as when riding on a subway or standing in some public place). He may drop to his knees praying and shouting in the midst of a crowd of people, or he may suddenly sit in a yoga position while in the midst of a crowd. He may make inappropriate sexual overtures or remarks to strangers.

Have you ever done anything that others might think unusual or that has called attention to yourself?

None	0 SS57
Questionable	1
Mild: Occasional instances of somewhat peculiar behavior	2
Moderate: Frequent instances of odd behavior	3
Marked: Very odd behavior	4
Severe: Extremely odd behavior which may have a fantastic quality	5

Aggressive and Agitated Behavior

The subject may behave in an aggressive, agitated manner, often quite unpredictably. He may start arguments inappropriately with friends or members of his family, or he may accost strangers on the street and begin haranguing them angrily. He may write letters of a threatening or angry nature to government officials or others with whom he has some quarrel. Occasionally, subjects may perform violent acts such as injuring or tormenting animals, or attempting to injure or kill human beings.

Have you ever done anything to try to harm animals or people?

Have you felt angry with anyone?

How did you express your anger?

Repetitive or Stereotyped Behavior

The subject may develop a set of repetitive actions or rituals that he must perform over and over. Frequently, he will attribute some symbolic significance to these actions and believe that they are either influencing others or preventing himself from being influenced. For example, he may eat jelly beans every night for dessert, assuming that different consequences will occur depending on the color of the jelly beans. He may have to eat foods in a particular order, wear particular clothes, or put them on in a certain order. He may have to write messages to himself or to others over and over; sometimes this will be in an unusual or occult language.

Are there any things that you feel you have to do?

None	0	SS58
Questionable	1	
Mild: Occasional instances	2	
Moderate: For example, writing angry letters to strangers	3	
Marked: For example, threatening people, public harangues	4	
Severe: For example, mutilating animals, attacking people	5	

None	0	SS59
Questionable	1	
Mild: Occasional instances of ritualistic or stereotyped behavior	2	
Moderate: For example, eating or dressing rituals lacking symbolic significance	3	
Marked: For example, eating or dressing rituals with a symbolic significance	4	
Severe: For example, keeping a diary in an incomprehensible language	5	

Global Rating of Severity of Bizarre Behavior

In making this rating, the interviewer should consider the type of behavior, the extent to which it deviates from social norms, the subject's awareness of the degree to which the behavior is deviant, and the extent to which it is obviously bizarre.

None	0	SS60
Questionable	1	
Mild: Occasional instances of unusual or apparently idiosyncratic behavior; subject usually has some insight	2	
Moderate: Behavior which is clearly deviant from social norms and seems somewhat bizarre; subject may have some insight	3	
Marked: Behavior which is markedly deviant from social norms and clearly bizarre; subject may have some insight	4	
Severe: Behavior which is extremely bizarre or fantastic; may include a single extreme act, e.g., attempting murder; subject usually lacks insight.	5	

POSITIVE FORMAL THOUGHT DISORDER

Positive formal thought disorder is fluent speech that tends to communicate poorly for a variety of reasons. The subject tends to skip from topic to topic without warning, to be distracted by events in the nearby environment, to join words together because they are semantically or phonologically alike even though they make no sense, or to ignore the question asked and ask another. This type of speech may be rapid, and it frequently seems quite disjointed. It has sometimes been referred to as "loose associations." Unlike alogia (negative formal thought disorder), a wealth of detail is provided, and the flow of speech tends to have an energetic, rather than an apathetic, quality to it.

In order to evaluate thought disorder, the subject should be permitted to talk at length on some topic, particularly a topic unrelated to his psychopathology, for as long as five to ten minutes. The interviewer should observe closely the extent to which his sequencing of ideas is well connected. In addition, the interviewer should insist that he clarify or elaborate further if the ideas seem vague or incomprehensible. He should also pay close attention to how well the subject can reply to a variety of different types of questions, ranging from simple (Where were you born?) to more complicated (How do you think the present government is doing?)

The anchor points for these ratings assume that the subject has been interviewed for a total of approximately forty-five minutes. If the interview is shorter, the ratings should be adjusted accordingly.

Derailment (Loose Associations)

A pattern of spontaneous speech in which the ideas slip off one track onto another which is clearly but obliquely related, or onto one which is completely unrelated. Things may be said in juxtaposition which lack a meaningful relationship, or the subject may shift idiosyncratically from one frame of reference to another. At times there may be a vague connection between the ideas, and at others none will be apparent. This pattern of speech is often characterized as sounding "disjointed." Perhaps the commonest manifestation of this disorder is a slow, steady slippage, with no single derailment being particularly severe, so that the speaker gets farther and farther off the track with each derailment without showing any awareness that his reply no longer has any connection with the question which was asked. This abnormality is often characterized by lack of cohesion between clauses and sentences and by unclear pronoun references.

None	0	SS61
Questionable	1	
Mild: Occasional instances of derailment, with only slight topic shifts	2	
Moderate: Several instances of derailment; subject is sometimes difficult to follow	3	
Marked: Frequent instances of derailment; subject is often difficult to follow	4	
Severe: Derailment so frequent and/or extreme that the subject's speech is almost incomprehensible	5	

Example: Interviewer: "Did you enjoy college?"

Subject: "Um-hum. Oh hey well, I oh, I really enjoyed some communities I tried it, and the, and the next day when I'd be going out, you know, um, I took control like uh, I put, um, bleach on my hair in, in California. My roommate was from Chicago, and she was going to the junior college. And we lived in the Y.M.C.A., so she wanted to put it, um, peroxide on my hair, and she did, and I got up and looked at the mirror and tears came to my eyes. Now do you understand it, I was fully aware of what was going on but why couldn't I, I . . . why, why the tears? I can't understand that, can you?"

Tangentiality

Replying to a question in an oblique, tangential or even irrelevant manner. The reply may be related to the question in some distant way. Or the reply may be unrelated and seem totally irrelevant. In the past tangentiality has sometimes been used as roughly equivalent to loose associations or derailment. The concept of tangentiality has been partially redefined so that it refers only to answers to questions and not to transitions in spontaneous speech.

Example: Interviewer: "What city are you from?"
Subject: "That's a hard question to answer because my parents . . . I was born in Iowa, but I know that I'm white instead of black, so apparently I came from the North somewhere and I don't know where, you know, I really don't know whether I'm Irish or Scandinavian or I don't, I don't believe I'm Polish but I think I'm, I think I might be German or Welsh."

None	0	SS62
Questionable	1	
Mild: One or two oblique replies	2	
Moderate: Occasional oblique replies (three to four times)	3	
Marked: Frequent oblique replies (more than four times)	4	
Severe: Tangentiality so severe that interviewing the subject is extremely difficult	5	

Incoherence (Word Salad, Schizophasia)

A pattern of speech which is essentially incomprehensible at times. Incoherence is often accompanied by derailment. It differs from derailment in that in incoherence the abnormality occurs within the level of the sentence or clause, which contains words or phrases that are joined incoherently. The abnormality in derailment involves unclear or confusing connections between larger units, such as sentences or clauses.

This type of language disorder is relatively rare. When it occurs, it tends to be severe or extreme, and mild forms are quite uncommon. It may sound quite similar to Wernicke's aphasia or jargon aphasia, and in these cases the disorder should only be called incoherence when history and laboratory data exclude the possibility of a past stroke, and formal testing for aphasia is negative.

Exclusions: Mildly ungrammatical constructions or idiomatic usages characteristic of particular regional or ethnic backgrounds, lack of education, or low intelligence.

Example: Interviewer: "What do you think about current political issues like the energy crisis?" Subject: "They're destroying too many cattle and oil just to make soap. If we need soap when you can jump into a pool of water, and then when you go to buy your gasoline, my folks always thought they should, get pop but the best thing to get, is motor oil, and, money. May, may as well go there and, trade in some, pop caps and, uh, tires, and tractors to group, car garages, so they can pull cars away from wrecks, is what I believed in."

None	0	SS63
Questionable	1	
Mild: Occasional instances of incoherence	2	
Moderate: Frequent bursts of incoherence	3	
Marked: At least half of the subject's speech is incomprehensible	4	
Severe: Almost all of the subject's speech is incomprehensible	5	

Illogicality

A pattern of speech in which conclusions are reached which do not follow logically. This may take the form of non-sequiturs (= it does not follow), in which the subject makes a logical inference between two clauses which is unwarranted or illogical. It may take the form of faulty inductive inferences. It may also take the form of reaching conclusions based on faulty premises without any actual delusional thinking.

Exclusions: Illogicality may either lead to or result from delusional beliefs. When illogical thinking occurs within the context of a delusional system, it should be subsumed under the concept of delusions and not considered a separate phenomenon representing a different type of thinking disorder. Illogical thinking which is clearly due to cultural or religious values or to intellectual deficit should also be excluded.

Example: "Parents are the people that raise you. Any thing that raises you can be a parent. Parents can be anything -- material, vegetable, or mineral -- that has taught you something. Parents would be the world of things that are alive, that are there. Rocks -- a person can look at a rock and learn something from it, so that would be a parent."

Circumstantiality

A pattern of speech which is very indirect and delayed in reaching its goal idea. In the process of explaining something, the speaker brings in many tedious details and sometimes makes parenthetical remarks. Circumstantial replies or statements may last for many minutes if the speaker is not interrupted and urged to get to the point. Interviewers will often recognize circumstantiality on the basis of needing to interrupt the speaker in order to complete the process of history-taking within an allotted time. When not called circumstantial, these people are often referred to as "long-winded."

Exclusions: Although it may coexist with instances of poverty of content of speech or loss of goal, it differs from poverty of content of speech in containing excessive amplifying or illustrative detail and from loss of goal in that the goal is eventually reached if the person is allowed to talk long enough. It differs from derailment in that the details presented are closely related to some particular goal or idea and that the particular goal or idea must be, by definition, eventually reached.

None	0 SS64
Questionable	1
Mild: Occasional instances of illogicality	2
Moderate: Frequent instances of illogicality (three or four times)	3
Marked: Much of the subject's speech is illogical (more than four times)	4
Severe: Most of the subject's speech is illogical	5

None	0 SS65
Questionable	1
Mild: Occasional instances of circumstantiality	2
Moderate: Frequent instances of circumstantiality	3
Marked: At least half of subject's speech is circumstantial	4
Severe: Most of the subject's speech is circumstantial	5

Pressure of Speech

An increase in the amount of spontaneous speech as compared to what is considered ordinary or socially customary. The subject talks rapidly and is difficult to interrupt. Some sentences may be left uncompleted because of eagerness to get on to a new idea. Simple questions which could be answered in only a few words or sentences are answered at great length so that the answer takes minutes rather than seconds and indeed may not stop at all if the speaker is not interrupted. Even when interrupted, the speaker often continues to talk. Speech tends to be loud and emphatic. Sometimes speakers with severe pressure will talk without any social stimulation and talk even though no one is listening. When subjects are receiving phenothiazines or lithium, their speech is often slowed down by medication, and then it can be judged only on the basis of amount, volume, and social appropriateness. If a quantitative measure is applied to the rate of speech, then a rate greater than 150 words per minute is usually considered rapid or pressured. This disorder may be accompanied by derailment, tangentiality, or incoherence, but it is distinct from them.

None	0	SS66
Questionable	1	
Mild: Slight pressure of speech; some slight increase in amount, speed, or loudness of speech	2	
Moderate: Usually takes several minutes to answer simple questions, may talk when no one is listening, and/or speaks loudly and rapidly	3	
Marked: Frequently talks as much as three minutes to answer simple questions; sometimes begins talking without social stimulation; difficult to interrupt	4	
Severe: Subject talks almost continually, cannot be interrupted at all, and/or may shout to drown out the speech of others	5	

Distractible Speech

During the course of a discussion or interview, the subject stops talking in the middle of a sentence or idea and changes the subject in response to a nearby stimulus, such as an object on a desk, the interviewer's clothing or appearance, etc.

Example: "Then I left San Francisco and moved to . . . where did you get that tie? It looks like it's left over from the 50's. I like the warm weather in San Diego. Is that a conch shell on your desk? Have you ever gone scuba diving?"

None	0	SS67
Questionable	1	
Mild: Is distracted once during an interview	2	
Moderate: Is distracted from two to four times during an interview	3	
Marked: Is distracted from five to ten times during an interview	4	
Severe: Is distracted more than ten times during an interview	5	

Clanging

A pattern of speech in which sounds rather than meaningful relationships appear to govern word choice, so that the intelligibility of the speech is impaired and redundant words are introduced. In addition to rhyming relationships, this pattern of speech may also include punning associations, so that a word similar in sound brings in a new thought.

Example: I'm not trying to make a noise. I'm trying to make sense. If you can make sense out of nonsense, well, have fun. I'm trying to make sense out of sense. I'm not making sense (cents) anymore. I have to make dollars."

Global Rating of Positive Formal Thought Disorder

In making this rating, the interviewer should consider the type of abnormality, the degree to which it affects the subject's ability to communicate, the frequency with which abnormal speech occurs, and its degree of severity.

None	0 SS68
Questionable	1
Mild: Occurs once during an interview	2
Moderate: Occurs from two to four times during an interview	3
Marked: Occurs five to ten times during an interview	4
Severe: Occurs more than ten times, or so frequently that the interview is incomprehensible.	

None	0 SS69
Questionable	1
Mild: Occasional instances of disorder; subject's speech is understandable	2
Moderate: Frequent instances of disorder; subject is sometimes hard to understand	3
Marked: Subject is often difficult to understand	4
Severe: Subject is incomprehensible	5

APPENDIX -IV



SCALE FOR THE ASSESSMENT OF NEGATIVE SYMPTOMS

(SANS)

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AFFECTIVE FLATTENING OR BLUNTING

Affective flattening or blunting manifests itself as a characteristic impoverishment of emotional expression, reactivity, and feeling. Affective flattening can be evaluated by observation of the subject's behavior and responsiveness during a routine interview. The rating of some items may be affected by drugs, since the Parkinsonian side-effect of phenothiazines may lead to mask-like facies and diminished associated movements. Other aspects of affect, such as responsivity or appropriateness, will not be affected, however.

Unchanging Facial Expression

The subject's face appears wooden, mechanical, frozen. It does not change expression, or changes less than normally expected, as the emotional content of discourse changes. Since phenothiazines may partially mimic this effect, the interviewer should be careful to note whether or not the subject is on medication, but should not try to "correct" the rating accordingly.

Not at all: Subject is normal or labile	0	SS11
Questionable decrease	1	
Mild: Occasionally the subject's expression is not as full as expected	2	
Moderate: Subject's expressions are dulled overall, but not absent	3	
Marked: Subject's face has a flat "set" look, but flickers of affect arise occasionally	4	
Severe: Subject's face looks "wooden" and changes little, if at all throughout the interview	5	

Decreased Spontaneous Movements

The subject sits quietly throughout the interview and shows few or no spontaneous movements. He does not shift position, move his legs, move his hands, etc., or does so less than normally expected.

Not at all: Subject moves normally or is overactive	0	SS12
Questionable decrease	1	
Mild: Some decrease in spontaneous movements	2	
Moderate: Subject moves three or four times during the interview	3	
Marked: Subject moves once or twice during the interview	4	
Severe: Subject sits immobile throughout the interview	5	

Paucity of Expressive Gestures

The subject does not use his body as an aid in expressing his ideas, through such means as hand gestures, sitting forward in his chair when intent on a subject, leaning back when relaxed, etc. This may occur in addition to decreased spontaneous movements.

Not at all: Subject uses expressive gestures normally or excessively	0	SS13
Questionable decrease	1	
Mild: Some decrease in expressive gestures	2	
Moderate: Subject uses body as an aid in expression at least three or four times	3	
Marked: Subject uses body as an aid in expression only once or twice	4	
Severe: Subject never uses body as an aid in expression	5	

Poor Eye Contact

The subject avoids looking at others or using his eyes as an aid in expression. He appears to be staring into space even when he is talking.

Not at all: Good eye contact and expression	0	SS14
Questionable decrease	1	
Mild: Some decrease in eye contact and eye expression	2	
Moderate: Subject's eye contact is decreased by at least half of normal	3	
Marked: Subject's eye contact is very infrequent	4	
Severe: Subject almost never looks at interviewer	5	

Affective Nonresponsivity

Failure to smile or laugh when prompted may be tested by smiling or joking in a way which would usually elicit a smile from a normal individual. The examiner may also ask, "Have you forgotten how to smile?" while smiling himself.

Not at all	0	SS15
Questionable decrease	1	
Mild: Slight but definite lack in responsivity	2	
Moderate: Subject occasionally seems to miss the cues to respond	3	
Marked: Subject seems to miss the cues to respond most of the time	4	
Severe: Subject is essentially unresponsive, even on prompting	5	

Lack of Vocal Inflections

While speaking the subject fails to show normal vocal emphasis patterns. Speech has a monotonic quality, and important words are not emphasized through changes in pitch or volume. Subject also may fail to change volume with changes of subject so that he does not drop his voice when discussing private topics nor raise it as he discusses things which are exciting or for which louder speech might be appropriate.

Not all all: Normal vocal inflections	0	SS16
Questionable decrease	1	
Mild: Slight decrease in vocal inflections	2	
Moderate: Interviewer notices several instances of flattened vocal inflections	3	
Marked: Obvious decrease in vocal inflections	4	
Severe: Subject's speech is a continuous monotone	5	

Global Rating of Affective Flattening

The global rating should focus on overall severity of affective flattening or blunting. Special emphasis should be given to such core features as unresponsiveness, inappropriateness, and an overall decrease in emotional intensity.

No flattening: Normal affect	0	SS17
Questionable affective flattening	1	
Mild affective flattening	2	
Moderate affective flattening	3	
Marked affective flattening	4	
Severe affective flattening	5	

Inappropriate Affect

Affect expressed is inappropriate or incongruous, not simply flat or blunted. Most typically, this manifestation of affective disturbance takes the form of smiling or assuming a silly facial expression while talking about a serious or sad subject. (Occasionally subjects may smile or laugh when talking about a serious subject which they find uncomfortable or embarrassing. Although their smiling may seem inappropriate, it is due to anxiety and therefore should not be rated as inappropriate affect.) Do not rate affective flattening or blunting as inappropriate.

Not at all: Affect is not inappropriate	0	SS18
Questionable	1	
Mild: At least one instance of inappropriate smiling or other inappropriate affect	2	
Moderate: Subject exhibits two to four instances of inappropriate affect	3	
Marked: Subject exhibits five to ten instances of inappropriate affect	4	
Severe: Subject's affect is inappropriate most of the time	5	

ALOGIA

Alogia is a general term coined to refer to the impoverished thinking and cognition that often occur in subjects with schizophrenia (Greek a = no, none; logos = mind, thought). Subjects with alogia have thinking processes that seem empty, turgid, or slow. Since thinking cannot be observed directly, it is inferred from the subject's speech. The two major manifestations of alogia are nonfluent empty speech (poverty of speech) and fluent empty speech (poverty of content of speech). Blocking and increased latency or response may also reflect alogia.

Poverty of Speech

Restriction in the amount of spontaneous speech, so that replies to questions tend to be brief, concrete, and unelaborated. Unprompted additional information is rarely provided. Replies may be monosyllabic, and some questions may be left unanswered altogether. When confronted with this speech pattern, the interviewer may find himself frequently prompting the subject in order to encourage elaboration of replies. To elicit this finding, the examiner must allow the subject adequate time to answer and to elaborate his answer.

No poverty of speech: A substantial and appropriate number of replies to questions include additional information	0	SS19
Questionable poverty of speech	1	
Mild: Occasional replies do not include elaborated information even though this is appropriate	2	
Moderate: Some replies do not include appropriately elaborated information, and some replies are monosyllabic or very brief--("Yes." "No." "Maybe." "I don't know." "Last week.")	3	
Marked: Answers are rarely more than a sentence or a few words in length	4	
Severe: Subject says almost nothing and occasionally fails to answer questions	5	

Poverty of Content of Speech

Although replies are long enough so that speech is adequate in amount, it conveys little information. Language tends to be vague, often over-abstract or over-concrete, repetitive, and stereotyped. The interviewer may recognize this finding by observing that the subject has spoken at some length but has not given adequate information to answer the question. Alternatively, the subject may provide enough information, but require many words to do so, so that a lengthy reply can be summarized in a sentence or two. Sometimes the interviewer may characterize the speech as "empty philosophizing."

Exclusions: This finding differs from circumstantiality in that the circumstantial subject tends to provide a wealth of detail.

Example: Interviewer: "Why is it, do you think, that people believe in God?" Subject: "Well, first of all because he uh, he are the person that is their personal savior. He walks with me and talks with me. And uh, the understanding that I have, um, a lot of peoples, they don't really, uh, know they own personal self. Because, uh, they ain't, they all, just don't know they personal self. They don't, know that he uh, seemed like to me, a lot of 'em don't understand that he walks and talks with them."

Blocking

Interruption of a train of speech before a thought or idea has been completed. After a period of silence which may last from a few seconds to minutes, the person indicates that she/he cannot recall what he had been saying or meant to say. Blocking should only be judged to be present if a person voluntarily describes losing his thought or if, upon questioning by the interviewer, the person indicates that that was the reason for pausing.

No poverty of content	0	SS20
Questionable	1	
Mild: Occasional replies are too vague to be comprehensible or can be markedly condensed	2	
Moderate: Frequent replies which are vague or can be markedly condensed to make up at least a quarter of the interview	3	
Marked: At least half of the subject's speech is composed of vague or incomprehensible replies	4	
Severe: Nearly all the speech is vague, incomprehensible, or can be markedly condensed	5	
No blocking	0	SS21
Questionable	1	
Mild: A single instance noted during a forty-five minute period	2	
Moderate: Occurs twice during forty-five minutes	3	
Marked: Occurs three or four times during forty-five minutes	4	
Severe: Occurs more than four times in forty-five minutes	5	

Increased Latency of Response

The subject takes a longer time to reply to questions than is usually considered normal. He may seem "distant" and sometimes the examiner may wonder if he has even heard the question. Prompting usually indicates that the subject is aware of the question, but has been having difficulty in formulating his thoughts in order to make an appropriate reply.

Not at all	0	SS22
Questionable	1	
Mild: Occasional brief pauses before replying	2	
Moderate: Often pauses several seconds before replying	3	
Marked: Usually pauses at least ten to fifteen seconds before replying	4	
Severe: Long pauses prior to nearly all replies.	5	

Global Rating of Alogia

Since the core features of alogia are poverty of speech and poverty of content of speech, the global rating should place particular emphasis on them.

No alogia	0	SS23
Questionable	1	
Mild: Mild but definite impoverishment in thinking	2	
Moderate: Significant evidence for impoverished thinking	3	
Marked: Subject's thinking seems impoverished much of the time	4	
Severe: Subject's thinking seems impoverished nearly all of the time	5	

AVOLITION-APATHY

Avolition manifests itself as a characteristic lack of energy, drive, and interest. Subjects are unable to mobilize themselves to initiate or persist in completing many different kinds of tasks. Unlike the diminished energy or interest of depression, the avolitional symptom complex in schizophrenia is usually not accompanied by saddened or depressed affect. The avolitional symptom complex often leads to severe social and economic impairment.

Grooming and Hygiene

The subject displays less attention to grooming and hygiene than normal. Clothing may appear sloppy, outdated, or soiled. The subject may bathe infrequently and not care for hair, nails, or teeth--leading to such manifestations as greasy or uncombed hair, dirty hands, body odor, or unclean teeth and bad breath. Overall, the appearance is dilapidated and disheveled. In extreme cases, the subject may even have poor toilet habits.

How often do you bathe or shower?

Do you change your clothes every day?

How often do you do laundry?

No evidence of poor grooming and hygiene	0	SS24
Questionable	1	
Mild: Some slight but definite indication of inattention to appearance, i.e., messy hair or disheveled clothes	2	
Moderate: Appearance is somewhat disheveled, i.e., greasy hair, dirty clothes	3	
Marked: Subject's attempts to keep up grooming or hygiene are minimal	4	
Severe: Subject's clothes, body and environment are dirty and smelly	5	

Impersistence at Work or School

The subject has had difficulty in seeking or maintaining

No evidence of impersistence at work

employment (or schoolwork) as appropriate for his or her age and sex. If a student, he/she does not do homework and may even fail to attend class. Grades will tend to reflect this. If a college student, there may be a pattern of registering for courses, but having to drop several or all of them before the semester is completed. If of working age, the subject may have found it difficult to work at a job because of inability to persist in completing tasks and apparent irresponsibility. He may go to work irregularly, wander away early, complete them in a disorganized manner. He may simply sit around the house and not seek any employment or seek it only in an infrequent and desultory manner. If a housewife or retired person, the subject may fail to complete chores, such as shopping or cleaning, or complete them in an apparently careless and half-hearted way.

Have you been having any problems at (work, school)?

Do you ever start some project and just never get around to finishing it?

Physical Anergia

The subject tends to be physically inert. He may sit in a chair for hours at a time and not initiate any spontaneous activity. If encouraged to become involved in an activity, he may participate only briefly and then wander away or disengage himself and return to sitting alone. He may spend large amounts of time in some relatively mindless and physically inactive task such as watching TV or playing solitaire. His family may report that he spends most of his time at home "doing nothing except sitting around". Either at home or in an inpatient setting he may spend much of his time sitting in his room.

Are there times when you lie or sit around most of the day?

(Does this ever last longer than one day?)

Global Rating of Avolition - Apathy

The global rating should reflect the overall severity of the avolition symptoms, given expectational norms for the subject's age and social status or origin. In making the global rating, strong weight may be given to only one or two prominent symptoms if they are particularly striking.

or school	0	SS25
Questionable	1	
Mild: Slight indications of impersistence, i.e., missing a couple days of school or work	2	
Moderate: Subject often has poor performance at work or school	3	
Marked: Subject has much difficulty maintaining even a below normal level of work or school	4	
Severe: Subject consistently fails to maintain a record at work or school	5	

No Evidence of Physical Anergia	0	SS26
Questionable	1	
Mild Anergia	2	
Moderate: Subject lies in bed or sits immobile at least a quarter of normal waking hours	3	
Marked: Subject lies in bed or sits immobile at least half of normal waking hours	4	
Severe: Subject lies in bed or sits immobile for most of the day	5	

No Avolition	0	SS27
Questionable	1	
Mild, But Definitely Present	2	
Moderate Avolition	3	
Marked Avolition	4	
Severe Avolition	5	

ANHEDONIA-ASOCIALITY

This symptom complex encompasses the schizophrenic subject's difficulties in experiencing interest or pleasure. It may express itself as a loss of interest in pleasurable activities, an inability to experience pleasure when participating in activities normally considered pleasurable, or a lack of involvement in social relationships of various kinds.

Recreational Interests and Activities

The subject may have few or no interests, activities, or hobbies. Although this symptom may begin insidiously or slowly, there will usually be some obvious decline from an earlier level of interest and activity. Subjects with relatively milder loss of interest will engage in some activities which are passive or non-demanding, such as watching TV, or will show only occasional or sporadic interest. Subjects with the most extreme loss will appear to have a complete and intractable inability to become involved in or enjoy activities. The rating in this area should take both the quality and quantity of recreational interests into account.

Have you felt interested in the things you usually enjoy?

(Have they been as fun as usual?)

Have you been watching TV or listening to the radio?

No Inability to Enjoy Recreational Interests or Activities	0	SS28
Questionable	1	
Mild Inability to Enjoy Recreational Activities	2	
Moderate: Subject often is not "up" for recreational activities	3	
Marked: Subject has little interest in and derives only mild pleasure from recreational activities	4	
Severe: Subject has no interest in and derives no pleasure from recreational activities	5	

Sexual Interest and Activity

The subject may show a decrement in sexual interest and activity, as judged by what would be normal for the subject's age and marital status. Individuals who are married may manifest disinterest in sex or may engage in intercourse only at the partner's request. In extreme cases, the subject may not engage in any sex at all. Single subjects may go for long periods of time without sexual involvement and make no effort to satisfy this drive. Whether married or single, they may report that they subjectively feel only minimal sex drive or that they take little enjoyment in sexual intercourse or in masturbatory activity even when they engage in it.

Have you noticed any changes in your sex drive?

No Inability to Enjoy Sexual Activities	0	SS29
Questionable Decrement in Sexual Interest and Activity	1	
Mild Decrement in Sexual Interest and Activity	2	
Moderate: Subject occasionally has noticed decreased interests in and/or enjoyment from sexual activities	3	
Marked: Subject has little interest in and/or derives little pleasure from sexual activities	4	
Severe: Subject has no interest in and/or derives no pleasure from sexual activities	5	

Ability to Feel Intimacy and Closeness

The subject may display an inability to form close and intimate relationships of a type appropriate for his age, sex, and family status. In the case of a younger person, this area should be rated in terms of relationships with the opposite sex and with parents and siblings. In the case of an older person who is married, the relationship with spouse and with children should be evaluated, while older unmarried individuals should be judged in terms of relationships with the opposite sex and any family members who live nearby. Subjects may display few or no feelings of affection to available family members. Or they may have arranged their lives so that they are completely isolated from any intimate relationships, living alone and making no effort to initiate contacts with family or members of the opposite sex.

Have you been having any problems with your (family, spouse)?

How would you feel about visiting with your (family, parents, spouse, etc.)?

No Inability to Feel Intimacy and Closeness	0	SS30
Questionable Inability	1	
Mild, But Definite Inability to Feel Intimacy and Closeness	2	
Moderate: Subject appears to enjoy family or significant others but does not appear to "look forward" to visits	3	
Marked: Subject appears neutral toward visits from family or significant others. Brightens only mildly	4	
Severe: Subject prefers no contact with or is hostile toward family or significant others	5	

Relationships with Friends and Peers

Subjects may also be relatively restricted in their relationships with friends and peers of either sex. They may have few or no friends, make little or no effort to develop such relationships, and choose to spend all or most of their time alone.

Have you been spending much time with friends?

Do you enjoy spending time alone, or would you rather have more friends?

No Inability to Form Close Friendships	0	SS31
Questionable Inability to Form Friendships	1	
Mild, But Definite Inability to Form Friendships	2	
Moderate: Subject able to interact, but sees friends/acquaintances only two to three times per month	3	
Marked: Subject has difficulty forming and/or keeping friendships. Sees friends/acquaintances only one to two times per month	4	
Severe: Subject has no friends and no interest in developing any social ties	5	

Global Rating of Anhedonia-Asociality

The global rating should reflect the overall severity of the anhedonia-asociality complex, taking into account the norms appropriate for the subject's age, sex, and family status.

No Evidence of Anhedonia-Asociality	0	SS32
Questionable Evidence of Anhedonia-Asociality	1	
Mild, But Definite Evidence of Anhedonia-Asociality	2	
Moderate Evidence of Anhedonia-Asociality	3	
Marked Evidence of Anhedonia-Asociality	4	
Severe Evidence of Anhedonia-Asociality	5	

ATTENTION

Attention is often poor in schizophrenics. The subject may have trouble focusing his attention, or he may only be able to focus sporadically and erratically. He may ignore attempts to converse with him, wander away while in the middle of an activity or task, or appear to be inattentive when engaged in formal testing or interviewing. He may or may not be aware of his difficulty in focusing his attention.

Social Inattentiveness

While involved in social situations or activities, the subject appears inattentive. He looks away during conversations, does not pick up the topic during a discussion, or appears uninvolved or unengaged. He may abruptly terminate a discussion or a task without any apparent reason. He may seem "spacy" or "out of it". He may seem to have poor concentration when playing games, reading, or watching TV.

No Indication of Inattentiveness	0	SS33
Questionable Signs	1	
Mild, But Definite Signs of Inattentiveness	2	
Moderate: Subject occasionally misses what is happening in the environment	3	
Marked: Subject often misses what is happening in the environment; has trouble with reading comprehension	4	
Severe: Subject unable to follow conversation, remember what he's read, or follow TV plot	5	

Inattentiveness During Mental Status Testing

The subject may perform poorly on simple tests of intellectual functioning in spite of adequate education and intellectual ability. This should be assessed by having the subject spell "world" backwards and by serial 7's (at least a tenth grade education) or serial 3's (at least a sixth grade education) for a series of five subtractions. A perfect score is 10.

No Errors	0	SS34
Questionable: No errors but subject performs in a halting manner or makes/corrects an error	1	
Mild, But Definite (One Error)	2	
Moderate (Two Errors)	3	
Marked (Three Errors)	4	
Severe (More Than Three Errors)	5	

Global Rating of Attention

This rating should assess the subject's overall ability to attend or concentrate, and include both clinical appearance and performance on tasks.

No Indications of Inattentiveness	0	SS35
Questionable	1	
Mild, But Definite Inattentiveness	2	
Moderate Inattentiveness	3	
Marked Inattentiveness	4	
Severe Inattentiveness	5	

APPENDIX - V



Brief Psychiatric Rating Scale (BPRS)

Expanded Version (4.0)

Introduction

This section reproduces an interview schedule, symptom definitions, and specific anchor points for rating symptoms on the BPRS. Clinicians intending to use the BPRS should also consult the detailed guidelines for administration contained in the reference below.

Scale Items and Anchor Points

Rate items 1-14 on the basis of individual's self-report. Note items 7, 12 and 13 are also rated on the basis of observed behaviour. Items 15-24 are rated on the basis of observed behaviour and speech.

1. Somatic Concern

Degree of concern over present bodily health. Rate the degree to which physical health is perceived as a problem by the individual, whether complaints have realistic bases or not. Somatic delusions should be rated in the severe range with or without somatic concern. Note: be sure to assess the degree of impairment due to somatic concerns only and not other symptoms, e.g., depression. In addition, if the individual rates 6 or 7 due to somatic delusions, then you must rate Unusual Thought Content at least 4 or above.

2 Very mild Occasional somatic concerns that tend to be kept to self.

3 Mild Occasional somatic concerns that tend to be voiced to others (e.g., family, doctor).

4 Moderate Frequent expressions of somatic concern or exaggerations of existing ills OR some preoccupation, but no impairment in functioning. Not delusional.

5 Moderately severe Frequent expressions of somatic concern or exaggerations of existing ills OR some preoccupation and moderate impairment of functioning. Not delusional.

6 Severe Preoccupation with somatic complaints with much impairment in functioning OR somatic delusions without acting on them or disclosing to others.

7 Extremely severe Preoccupation with somatic complaints with severe impairment in functioning OR somatic delusions that tend to be acted on or disclosed to others.

"Have you been concerned about your physical health?" "Have you had any physical illness or seen a medical doctor lately? (What does your doctor say is wrong? How serious is it?)"

"Has anything changed regarding your appearance?"

"Has it interfered with your ability to perform your usual activities and/or work?"

"Did you ever feel that parts of your body had changed or stopped working?"

[If individual reports any somatic concerns/delusions, ask the following]:

"How often are you concerned about [use individual's description]?"

"Have you expressed any of these concerns to others?"

2. Anxiety

Reported apprehension, tension, fear, panic or worry. Rate only the individual's statements - not observed anxiety which is rated under Tension.

2 Very mild Reports some discomfort due to worry OR infrequent worries that occur more than usual for most normal individuals.

3 Mild Worried frequently but can readily turn attention to other things.

4 Moderate Worried most of the time and cannot turn attention to other things easily but no impairment in functioning OR occasional anxiety with autonomic accompaniment but no impairment in functioning.

5 Moderately Severe Frequent, but not daily, periods of anxiety with autonomic accompaniment OR some areas of functioning are disrupted by anxiety or worry.

6 Severe Anxiety with autonomic accompaniment daily but not persisting throughout the day OR many areas of functioning are disrupted by anxiety or constant worry.

7 Extremely Severe Anxiety with autonomic accompaniment persisting throughout the day OR most areas of functioning are disrupted by anxiety or constant worry.

"Have you been worried a lot during [mention time frame]? Have you been nervous or apprehensive? (What do you worry about?)"

"Are you concerned about anything? How about finances or the future?"

"When you are feeling nervous, do your palms sweat or does your heart beat fast (or shortness of breath, trembling, choking)?"

[If individual reports anxiety or autonomic accompaniment, ask the following]:

"How much of the time have you been [use individual's description]?"

"Has it interfered with your ability to perform your usual activities/work?"

3. Depression

Include sadness, unhappiness, anhedonia and preoccupation with depressing topics (can't attend to TV or conversations due to depression), hopeless, loss of self-esteem (dissatisfied or disgusted with self or feelings of worthlessness). Do not include vegetative symptoms, e.g., motor retardation, early waking or the amotivation that accompanies the deficit syndrome.

2 Very mild Occasionally feels sad, unhappy or depressed.

3 Mild Frequently feels sad or unhappy but can readily turn attention to other things.

4 Moderate Frequent periods of feeling very sad, unhappy, moderately depressed, but able to function with extra effort.

5 Moderately Severe Frequent, but not daily, periods of deep depression OR some areas of functioning are disrupted by depression.

6 Severe Deeply depressed daily but not persisting throughout the day OR many areas of functioning are disrupted by depression.

7 Extremely Severe Deeply depressed daily OR most areas of functioning are disrupted by depression.

"How has your mood been recently? Have you felt depressed (sad, down, unhappy, as if you didn't care)?"

"Are you able to switch your attention to more pleasant topics when you want to?"

"Do you find that you have lost interest in or get less pleasure from things you used to enjoy, like family, friends, hobbies, watching TV, eating?"

[If individual reports feelings of depression, ask the following]:

"How long do these feelings last?" "Has it interfered with your ability to perform your usual activities?"

4. Suicidality

Expressed desire, intent, or actions to harm or kill self.

2 Very mild Occasional feelings of being tired of living. No overt suicidal thoughts.

3 Mild Occasional suicidal thoughts without intent or specific plan OR he/she feels they would be better off dead.

4 Moderate Suicidal thoughts frequent without intent or plan.

5 Moderately Severe Many fantasies of suicide by various methods. May seriously consider making an attempt with specific time and plan OR impulsive suicide attempt using non-lethal method or in full view of potential saviours.

6 Severe Clearly wants to kill self. Searches for appropriate means and time, OR potentially serious suicide attempt with individual knowledge of possible rescue.

7 Extremely Severe Specific suicidal plan and intent (e.g., "as soon as _____ I will do it by doing X"), OR suicide attempt characterised by plan individual thought was lethal or attempt in secluded environment.

"Have you felt that life wasn't worth living? Have you thought about harming or killing yourself? Have you felt tired of living or as though you would be better off dead? Have you ever felt like ending it all?"

[If individual reports suicidal ideation, ask the following]:

"How often have you thought about [use individual's description]?"

"Did you (Do you) have a specific plan?"

5. Guilt

Overconcern or remorse for past behaviour. Rate only individual's statements, do not infer guilt feelings from depression, anxiety, or neurotic defences. Note: if the individual rates 6 or 7 due to delusions of guilt, then you must rate Unusual Thought Content at least 4 or above, depending on level of preoccupation and impairment.

2 Very mild Concerned about having failed someone, or at something, but not preoccupied. Can shift thoughts to other matters easily.

3 Mild Concerned about having failed someone, or at something, with some preoccupation. Tends to voice guilt to others.

4 Moderate Disproportionate preoccupation with guilt, having done wrong, injured others by doing or failing to do something, but can readily turn attention to other things.

5 Moderately Severe Preoccupation with guilt, having failed someone or at something, can turn attention to other things, but only with great effort. Not delusional.

6 Severe Delusional guilt OR unreasonable self-reproach very out of proportion to circumstances. Moderate preoccupation present.

7 Extremely Severe Delusional guilt OR unreasonable self-reproach grossly out of proportion to circumstances. Individual is very preoccupied with guilt and is likely to disclose to others or act on delusions.

"Is there anything you feel guilty about? Have you been thinking about past problems?"

"Do you tend to blame yourself for things that have happened?"

"Have you done anything you're still ashamed of?"

[If individual reports guilt/remorse/delusions, ask the following]:

"How often have you been thinking about [use individual's description]?"

"Have you disclosed your feelings of guilt to others?"

6. Hostility

Animosity, contempt, belligerence, threats, arguments, tantrums, property destruction, fights, and any other expression of hostile attitudes or actions. Do not infer hostility from neurotic defences, anxiety or somatic complaints. Do not include incidents of appropriate anger or obvious self-defence.

2 Very mild Irritable or grumpy, but not overtly expressed.

3 Mild Argumentative or sarcastic.

4 Moderate Overtly angry on several occasions OR yelled at others excessively.

5 Moderately Severe Has threatened, slammed about or thrown things.

6 Severe Has assaulted others but with no harm likely, e.g., slapped or pushed, OR destroyed property, e.g., knocked over furniture, broken windows.

7 Extremely Severe Has attacked others with definite possibility of harming them or with actual harm, e.g., assault with hammer or weapon.

"How have you been getting along with people (family, co-workers, etc.)?"

"Have you been irritable or grumpy lately? (How do you show it? Do you keep it to yourself?"

"Were you ever so irritable that you would shout at people or start fights or arguments? (Have you found yourself yelling at people you didn't know?)"

"Have you hit anyone recently?"

7. Elevated Mood

A pervasive, sustained and exaggerated feeling of well-being, cheerfulness, euphoria (implying a pathological mood), optimism that is out of proportion to the circumstances. Do not infer elation from increased activity or from grandiose statements alone.

2 Very mild Seems to be very happy, cheerful without much reason.

3 Mild Some unaccountable feelings of well-being that persist.

4 Moderate Reports excessive or unrealistic feelings of well-being, cheerfulness, confidence or optimism inappropriate to circumstances, some of the time. May frequently joke, smile, be giddy, or overly enthusiastic OR few instances of marked elevated mood with euphoria.

5 Moderately Severe Reports excessive or unrealistic feelings of well-being, confidence or optimism inappropriate to circumstances, much of the time. May describe feeling 'on top of the world', 'like everything is falling into place', or 'better than ever before', OR several instances of marked elevated mood with euphoria.

6 Severe Reports many instances of marked elevated mood with euphoria OR mood definitely elevated almost constantly throughout interview and inappropriate to content.

7 Extremely Severe Individual reports being elated or appears almost intoxicated, laughing, joking, giggling, constantly euphoric, feeling invulnerable, all inappropriate to immediate circumstances.

"Have you felt so good or high that other people thought that you were not your normal self?" "Have you been feeling cheerful and 'on top of the world' without any reason?"

[If individual reports elevated mood/euphoria, ask the following]:

"Did it seem like more than just feeling good?"

"How long did that last?"

8. Grandiosity

Exaggerated self-opinion, self-enhancing conviction of special abilities or powers or identity as someone rich or famous. Rate only individual's statements about himself, not his/her demeanour. Note: if the individual rates 6 or 7 due to grandiose delusions, you must rate Unusual Thought Content at least 4 or above.

2 Very mild Feels great and denies obvious problems, but not unrealistic.

3 Mild Exaggerated self-opinion beyond abilities and training.

4 Moderate Inappropriate boastfulness, e.g., claims to be brilliant, insightful or gifted beyond realistic proportions, but rarely self-discloses or acts on these inflated self-concepts. Does not claim that grandiose accomplishments have actually occurred.

5 Moderately Severe Same as 4 but often self-discloses and acts on these grandiose ideas. May have doubts about the reality of the grandiose ideas. Not delusional.

6 Severe Delusional - claims to have special powers like ESP, to have millions of dollars, invented new machines, worked at jobs when it is known that he/she was never employed in these capacities, be Jesus Christ, or the Prime Minister. Individual may not be very preoccupied.

7 Extremely Severe Delusional - same as 6 but individual seems very preoccupied and tends to disclose or act on grandiose delusions.

"Is there anything special about you? Do you have any special abilities or powers? Have you thought that you might be somebody rich or famous?"

[If the individual reports any grandiose ideas/delusions, ask the following]:

"How often have you been thinking about [use individual's description]? Have you told anyone about what you have been thinking? Have you acted on any of these ideas?"

9. Suspiciousness

Expressed or apparent belief that other persons have acted maliciously or with discriminatory intent. Include persecution by supernatural or other non-human agencies (e.g., the devil). Note: ratings of 3 or above should also be rated under Unusual Thought Content.

2 Very mild Seems on guard. Reluctant to respond to some 'personal' questions. Reports being overly self-conscious in public.

3 Mild Describes incidents in which others have harmed or wanted to harm him/her that sound plausible. Individual feels as if others are watching, laughing or criticising him/her in public, but this occurs only occasionally or rarely. Little or no preoccupation.

4 Moderate Says other persons are talking about him/her maliciously, have negative intentions or may harm him/her. Beyond the likelihood of plausibility, but not delusional. Incidents of suspected persecution occur occasionally (less than once per week) with some preoccupation.

5 Moderately Severe Same as 4, but incidents occur frequently, such as more than once per week. Individual is moderately preoccupied with ideas of persecution OR individual reports persecutory delusions expressed with much doubt (e.g., partial delusion).

6 Severe Delusional - speaks of Mafia plots, the FBI or others poisoning his/her food, persecution by supernatural forces.

7 Extremely Severe Same as 6, but the beliefs are bizarre or more preoccupying. Individual tends to disclose or act on persecutory delusions.

"Do you ever feel uncomfortable in public? Does it seem as though others are watching you? Are you concerned about anyone's intentions toward you? Is anyone going out of their way to give you a hard time, or trying to hurt you? Do you feel in any danger?"

[If individual reports any persecutory ideas/delusions, ask the following]:

"How often have you been concerned that [use individual's description]? Have you told anyone about these experiences?"

10. Hallucinations

Reports of perceptual experiences in the absence of relevant external stimuli. When rating degree to which functioning is disrupted by hallucinations, include preoccupation with the content and experience of the hallucinations, as well as functioning disrupted by acting out on the hallucinatory content (e.g., engaging in deviant behaviour due to command hallucinations). Include thoughts aloud ('gedenkenloutwerden') or pseudohallucinations (e.g., hears a voice inside head) if a voice quality is present.

2 Very mild While resting or going to sleep, sees visions, smells odours or hears voices, sounds, or whispers in the absence of external stimulation, but no impairment in functioning.

3 Mild While in a clear state of consciousness, hears a voice calling the individual's name, experiences non-verbal auditory hallucinations (e.g., sounds or whispers), formless visual hallucinations or has sensory experiences in the presence of a modality-relevant stimulus (e.g., visual illusions) infrequently (e.g., 1-2 times per week) and with no functional impairment.

4 Moderate Occasional verbal, visual, gustatory, olfactory or tactile hallucinations with no functional impairment OR non-verbal auditory hallucinations/visual illusions more than infrequently or with impairment.

5 Moderately Severe Experiences daily hallucinations OR some areas of functioning are disrupted by hallucinations.

6 Severe Experiences verbal or visual hallucinations several times a day OR many areas of functioning are disrupted by these hallucinations.

7 Extremely Severe Persistent verbal or visual hallucinations throughout the day OR most areas of functioning are disrupted by these hallucinations.

"Do you ever seem to hear your name being called?"

"Have you heard any sounds or people talking to you or about you when there has been nobody around?"

[If hears voices]:

"What does the voice/voices say? Did it have a voice quality?"

"Do you ever have visions or see things that others do not see? What about smell odours that others do not smell?"

[If the individual reports hallucinations, ask the following]:

"Have these experiences interfered with your ability to perform your usual activities/work? How do you explain them? How often do they occur?"

11. Unusual thought content

Unusual, odd, strange, or bizarre thought content. Rate the degree of unusualness, not the degree of disorganisation of speech. Delusions are patently absurd, clearly false or bizarre ideas that are expressed with full conviction. Consider the individual to have full conviction if he/she has acted as though the delusional belief was true. Ideas of reference/persecution can be differentiated from delusions in that ideas are expressed with much doubt and contain more elements of reality. Include thought insertion, withdrawal and broadcast. Include grandiose, somatic and persecutory delusions even if rated elsewhere. Note: if Somatic Concern, Guilt, Suspiciousness or Grandiosity are rated 6 or 7 due to delusions, then Unusual Thought Content must be rated 4 or above.

2 Very mild Ideas of reference (people may stare or may laugh at him), ideas of persecution (people may mistreat him). Unusual beliefs in psychic powers, spirits, UFOs, or unrealistic beliefs in one's own abilities. Not strongly held. Some doubt.

3 Mild Same as 2, but degree of reality distortion is more severe as indicated by highly unusual ideas or greater conviction. Content may be typical of delusions (even bizarre), but without full conviction. The delusion does not seem to have fully formed, but is considered as one possible explanation for an unusual experience.

4 Moderate Delusion present but no preoccupation or functional impairment. May be an encapsulated delusion or a firmly endorsed absurd belief about past delusional circumstances.

5 Moderately Severe Full delusion(s) present with some preoccupation OR some areas of functioning disrupted by delusional thinking.

6 Severe Full delusion(s) present with much preoccupation OR many areas of functioning are disrupted by delusional thinking.

7 Extremely Severe Full delusion(s) present with almost total preoccupation OR most areas of functioning disrupted by delusional thinking.

"Have you been receiving any special messages from people or from the way things are arranged around you? Have you seen any references to yourself on TV or in the newspapers?"

"Can anyone read your mind?"

"Do you have a special relationship with God?"

"Is anything like electricity, X-rays, or radio waves affecting you?"

"Are thoughts put into your head that are not your own?"

"Have you felt that you were under the control of another person or force?"

[If individual reports any odd ideas/delusions, ask the following]:

"How often do you think about [use individual's description]?"

"Have you told anyone about these experiences? How do you explain the things that have been happening [specify]?"

Rate items 12-13 on the basis of individual's self-report and observed behaviour.

12. Bizarre behaviour

Reports of behaviours which are odd, unusual, or psychotically criminal. Not limited to interview period. Include inappropriate sexual behaviour and inappropriate affect.

2 Very mild Slightly odd or eccentric public behaviour, e.g., occasionally giggles to self, fails to make appropriate eye contact, that does not seem to attract the attention of others OR unusual behaviour conducted in private, e.g., innocuous rituals, that would not attract the attention of others.

3 Mild Noticeably peculiar public behaviour, e.g., inappropriately loud talking, makes inappropriate eye contact, OR private behaviour that occasionally, but not always, attracts the attention of others, e.g., hoards food, conducts unusual rituals, wears gloves indoors.

4 Moderate Clearly bizarre behaviour that attracts or would attract (if done privately) the attention or concern of others, but with no corrective intervention necessary. Behaviour occurs occasionally, e.g., fixated staring into space for several minutes, talks back to voices once, inappropriate giggling/laughter on 1-2 occasions, talking loudly to self.

5 Moderately Severe Clearly bizarre behaviour that attracts or would attract (if done privately) the attention of others or the authorities, e.g., fixated staring in a socially disruptive way, frequent inappropriate giggling/laughter, occasionally responds to voices, or eats non-foods.

6 Severe Bizarre behaviour that attracts attention of others and intervention by authorities, e.g., directing traffic, public nudity, staring into space for long periods, carrying on a conversation with hallucinations, frequent inappropriate giggling/laughter.

7 Extremely Severe Serious crimes committed in a bizarre way that attract the attention of others and the control of authorities, e.g., sets fires and stares at flames OR almost constant bizarre behaviour, e.g., inappropriate giggling/laughter, responds only to hallucinations and cannot be engaged in interaction.

"Have you done anything that has attracted the attention of others?"

"Have you done anything that could have gotten you into trouble with the police?"

"Have you done anything that seemed unusual or disturbing to others?"

13. Self-neglect

Hygiene, appearance, or eating behaviour below usual expectations, below socially acceptable standards or life threatening.

2 Very mild Hygiene/appearance slightly below usual community standards, e.g., shirt out of pants, buttons unbuttoned, shoe laces untied, but no social or medical consequences.

3 Mild Hygiene/appearance occasionally below usual community standards, e.g., irregular bathing, clothing is stained, hair uncombed, occasionally skips an important meal. No social or medical consequences.

4 Moderate Hygiene/appearance is noticeably below usual community standards, e.g., fails to bathe or change clothes, clothing very soiled, hair unkempt, needs prompting, noticeable by others OR irregular eating and drinking with minimal medical concerns and consequences.

5 Moderately Severe Several areas of hygiene/appearance are below usual community standards OR poor grooming draws criticism by others and requires regular prompting. Eating or hydration are irregular and poor, causing some medical problems.

6 Severe Many areas of hygiene/appearance are below usual community standards, does not always bathe or change clothes even if prompted. Poor grooming has caused social ostracism at school/residence/work, or required intervention. Eating erratic and poor, may require medical intervention.

7 Extremely Severe Most areas of hygiene/appearance/nutrition are extremely poor and easily noticed as below usual community standards OR hygiene/appearance/nutrition require urgent and immediate medical intervention.

"How has your grooming been lately? How often do you change your clothes? How often do you take showers? Has anyone (parents/staff) complained about your grooming or dress? Do you eat regular meals?"

14. Disorientation

Does not comprehend situations or communications, such as questions asked during the entire BPRS interview. Confusion regarding person, place, or time. Do not rate if incorrect responses are due to delusions.

2 Very mild Seems muddled or mildly confused 1-2 times during interview. Oriented to person, place and time.

3 Mild Occasionally muddled or mildly confused 3-4 times during interview. Minor inaccuracies in person, place, or time, e.g., date off by more than 2 days, or gives wrong division of hospital or community centre.

4 Moderate Frequently confused during interview. Minor inaccuracies in person, place, or time are noted, as in 3 above. In addition, may have difficulty remembering general information, e.g., name of Prime Minister.

5 Moderately Severe Markedly confused during interview, or to person, place, or time. Significant inaccuracies are noted, e.g., date off by more than one week, or cannot give correct name of hospital. Has difficulty remembering personal information, e.g., where he/she was born or recognising familiar people.

6 Severe Disoriented as to person, place, or time, e.g., cannot give correct month and year. Disoriented in 2 out of 3 spheres.

7 Extremely Severe Grossly disoriented as to person, place, or time, e.g., cannot give name or age. Disoriented in all three spheres.

"May I ask you some standard questions we ask everybody?"

"How old are you? What is the date [allow 2 days]"

"What is this place called? What year were you born? Who is the Prime Minister?"

Rate items 15-24 on the basis of observed behaviour and speech.

15 Conceptual disorganisation

Degree to which speech is confused, disconnected, vague or disorganised. Rate tangentiality, circumstantiality, sudden topic shifts, incoherence, derailment, blocking, neologisms, and other speech disorders. Do not rate content of speech.

2 Very mild Peculiar use of words or rambling but speech is comprehensible.

3 Mild Speech a bit hard to understand or make sense of due to tangentiality, circumstantiality, or sudden topic shifts.

4 Moderate Speech difficult to understand due to tangentiality, circumstantiality, idiosyncratic speech, or topic shifts on many occasions OR 1-2 instances of incoherent phrases.

5 Moderately Severe Speech difficult to understand due to circumstantiality, tangentiality, neologisms, blocking or topic shifts most of the time, OR 3-5 instances of incoherent phrases.

6 Severe Speech is incomprehensible due to severe impairment most of the time. Many BPRS items cannot be rated by self-report alone.

7 Extremely Severe Speech is incomprehensible throughout interview.

16. Blunted affect

Restricted range in emotional expressiveness of face, voice, and gestures. Marked indifference or flatness even when discussing distressing topics. In the case of euphoric or dysphoric individuals, rate Blunted Affect if a flat quality is also clearly present.

2 Very mild Emotional range is slightly subdued or reserved but displays appropriate facial expressions and tone of voice that are within normal limits.

3 Mild Emotional range overall is diminished, subdued or reserved, without many spontaneous and appropriate emotional responses. Voice tone is slightly monotonous.

4 Moderate Emotional range is noticeably diminished, individual doesn't show emotion, smile or react to distressing topics except infrequently. Voice tone is monotonous or

there is noticeable decrease in spontaneous movements. Displays of emotion or gestures are usually followed by a return to flattened affect.

5 Moderately Severe Emotional range very diminished, individual doesn't show emotion, smile, or react to distressing topics except minimally, few gestures, facial expression does not change very often. Voice tone is monotonous much of the time.

6 Severe Very little emotional range or expression. Mechanical in speech and gestures most of the time. Unchanging facial expression. Voice tone is monotonous most of the time.

7 Extremely Severe Virtually no emotional range or expressiveness, stiff movements. Voice tone is monotonous all of the time.

Use the following probes at end of interview to assess emotional responsivity:

"Have you heard any good jokes lately? Would you like to hear a joke?"

17. Emotional withdrawal

Deficiency in individual's ability to relate emotionally during interview situation. Use your own feeling as to the presence of an 'invisible barrier' between individual and interviewer. Include withdrawal apparently due to psychotic processes.

2 Very mild Lack of emotional involvement shown by occasional failure to make reciprocal comments, appearing preoccupied, or smiling in a stilted manner, but spontaneously engages the interviewer most of the time.

3 Mild Lack of emotional involvement shown by noticeable failure to make reciprocal comments, appearing preoccupied, or lacking in warmth, but responds to interviewer when approached.

4 Moderate Emotional contact not present much of the interview because individual does not elaborate responses, fails to make eye contact, doesn't seem to care if interviewer is listening, or may be preoccupied with psychotic material.

5 Moderately Severe Same as 4 but emotional contact not present most of the interview.

6 Severe Actively avoids emotional participation. Frequently unresponsive or responds with yes/no answers (not solely due to persecutory delusions). Responds with only minimal affect.

7 Extremely Severe Consistently avoids emotional participation. Unresponsive or responds with yes/no answers (not solely due to persecutory delusions). May leave during interview or just not respond at all.

18. Motor retardation

Reduction in energy level evidenced by slowed movements and speech, reduced body tone, decreased number of spontaneous body movements. Rate on the basis of observed behaviour of the individual only. Do not rate on the basis of individual's subjective impression of his own energy level. Rate regardless of medication effects.

2 Very mild Slightly slowed or reduced movements or speech compared to most people.

3 Mild Noticeably slowed or reduced movements or speech compared to most people.

4 Moderate Large reduction or slowness in movements or speech.

5 Moderately Severe Seldom moves or speaks spontaneously OR very mechanical or stiff movements

6 Severe Does not move or speak unless prodded or urged.

7 Extremely Severe Frozen, catatonic.

19. Tension

Observable physical and motor manifestations of tension, 'nervousness' and agitation. Self-reported experiences of tension should be rated under the item on anxiety. Do not rate if restlessness is solely akathisia, but do rate if akathisia is exacerbated by tension.

2 Very mild More fidgety than most but within normal range. A few transient signs of tension, e.g., picking at fingernails, foot wagging, scratching scalp several times or finger tapping.

3 Mild Same as 2, but with more frequent or exaggerated signs of tension.

4 Moderate Many and frequent signs of motor tension with one or more signs sometimes occurring simultaneously, e.g., wagging one's foot while wringing hands together. There are times when no signs of tension are present.

5 Moderately Severe Many and frequent signs of motor tension with one or more signs often occurring simultaneously. There are still rare times when no signs of tension are present.

6 Severe Same as 5, but signs of tension are continuous.

7 Extremely Severe Multiple motor manifestations of tension are continuously present, e.g., continuous pacing and hand wringing.

20. Unco-operativeness

Resistance and lack of willingness to co-operate with the interview. The unco-operativeness might result from suspiciousness. Rate only unco-operativeness in relation to the interview, not behaviours involving peers and relatives.

2 Very mild Shows non-verbal signs of reluctance, but does not complain or argue.

3 Mild Gripes or tries to avoid complying, but goes ahead without argument.

4 Moderate Verbally resists but eventually complies after questions are rephrased or repeated.

5 Moderately Severe Same as 4, but some information necessary for accurate ratings is withheld.

6 Severe Refuses to co-operate with interview, but remains in interview situation.

7 Extremely Severe Same as 6, with active efforts to escape the interview

21. Excitement

Heightened emotional tone or increased emotional reactivity to interviewer or topics being discussed, as evidenced by increased intensity of facial expressions, voice tone, expressive gestures or increase in speech quantity and speed.

2 Very mild Subtle and fleeting or questionable increase in emotional intensity. For example, at times seems keyed-up or overly alert.

3 Mild Subtle but persistent increase in emotional intensity. For example, lively use of gestures and variation in voice tone.

4 Moderate Definite but occasional increase in emotional intensity. For example, reacts to interviewer or topics that are discussed with noticeable emotional intensity. Some pressured speech.

5 Moderately Severe Definite and persistent increase in emotional intensity. For example, reacts to many stimuli, whether relevant or not, with considerable emotional intensity. Frequent pressured speech.

6 Severe Marked increase in emotional intensity. For example, reacts to most stimuli with inappropriate emotional intensity. Has difficulty settling down or staying on task. Often restless, impulsive, or speech is often pressured.

7 Extremely Severe Marked and persistent increase in emotional intensity. Reacts to all stimuli with inappropriate intensity, impulsiveness. Cannot settle down or stay on task. Very restless and impulsive most of the time. Constant pressured speech.

22. Distractibility

Degree to which observed sequences of speech and actions are interrupted by stimuli unrelated to the interview. Distractibility is rated when the individual shows a change in the focus of attention as characterised by a pause in speech or a marked shift in gaze. Individual's attention may be drawn to noise in adjoining room, books on a shelf, interviewer's clothing, etc. Do not rate circumstantiality, tangentiality or flight of ideas. Also, do not rate rumination with delusional material. Rate even if the distracting stimulus cannot be identified.

2 Very mild Generally can focus on interviewer's questions with only 1 distraction or inappropriate shift of attention of brief duration.

3 Mild Individual shifts focus of attention to matters unrelated to the interview 2-3 times.

4 Moderate Often responsive to irrelevant stimuli in the room, e.g., averts gaze from the interviewer.

5 Moderately Severe Same as above, but now distractibility clearly interferes with the flow of the interview.

6 Severe Extremely difficult to conduct interview or pursue a topic due to preoccupation with irrelevant stimuli.

7 Extremely Severe Impossible to conduct interview due to preoccupation with irrelevant stimuli.

23. Motor hyperactivity

Increase in energy level evidenced in more frequent movement and/or rapid speech. Do not rate if restlessness is due to akathisia.

2 Very mild Some restlessness, difficulty sitting still, lively facial expressions, or somewhat talkative

3 Mild Occasionally very restless, definite increase in motor activity, lively gestures, 1-3 brief instances of pressured speech.

4 Moderate Very restless, fidgety, excessive facial expressions, or non-productive and repetitious motor movements. Much pressured speech, up to one-third of the interview.

5 Moderately Severe Frequently restless, fidgety. Many instances of excessive non-productive and repetitious motor movements. On the move most of the time. Frequent pressured speech, difficult to interrupt. Rises on 1-2 occasions to pace.

6 Severe Excessive motor activity, restlessness, fidgety, loud tapping, noisy, etc., throughout most of the interview. Speech can only be interrupted with much effort. Rises on 3-4 occasions to pace.

7 Extremely Severe Constant excessive motor activity throughout entire interview, e.g., constant pacing, constant pressured speech with no pauses, individual can only be interrupted briefly and only small amounts of relevant information can be obtained

24. Mannerisms and posturing

Unusual and bizarre behaviour, stylised movements or acts, or any postures which are clearly uncomfortable or inappropriate. Exclude obvious manifestations of medication side effects. Do not include nervous mannerisms that are not odd or unusual.

2 Very mild Eccentric or odd mannerisms or activity that ordinary persons would have difficulty explaining, e.g., grimacing, picking. Observed once for a brief period.

3 Mild Same as 2, but occurring on two occasions of brief duration.

4 Moderate Mannerisms or posturing, e.g., stylised movements or acts, rocking, nodding, rubbing, or grimacing, observed on several occasions for brief periods or infrequently but very odd. For example, uncomfortable posture maintained for 5 seconds more than twice.

5 Moderately Severe Same as 4, but occurring often, or several examples of very odd mannerisms or posturing that are idiosyncratic to the individual.

6 Severe Frequent stereotyped behaviour, assumes and maintains uncomfortable or inappropriate postures, intense rocking, smearing, strange rituals or foetal posturing. Individual can interact with people and the environment for brief periods despite these behaviours.

7 Extremely Severe Same as 6, but individual cannot interact with people or the environment due to these behaviours.

APPENDIX -VI



SIMPSON-ANGUS EXTRAPYRAMIDAL SIDE EFFECTS SCALE

The exam should be conducted in a room where the subject can walk a sufficient distance to allow him/her to get into a natural rhythm (e.g. 15 paces). Each side of the body should be examined. If one side shows more pronounced pathology than the other, this score should be noted and this taken. Cogwheel rigidity may be palpated when the examination is carried out for items 3, 4, 5, and 6. It is not rated separately and is merely another way to detect rigidity. It would indicate that a minimum score of 1 would be mandatory.

1. **Gait:** The patient is examined as he walks into the examining room, his gait, the swing of his arms, his general posture, all form the basis for an overall score for this item. This is rated as follows:
 - 0 Normal
 - 1 Diminution in swing while the patient is walking
 - 2 Marked diminution in swing with obvious rigidity in the arm
 - 3 Stiff gait with arms held rigidly before the abdomen
 - 4 Stooped shuffling gait with propulsion and retropulsion
2. **Arm Dropping:** The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject, a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly:
 - 0 Normal, free fall with loud slap and rebound
 - 1 Fall slowed slightly with less audible contact and little rebound
 - 2 Fall slowed, no rebound
 - 3 Marked slowing, no slap at all
 - 4 Arms fall as though against resistance; as though through glue
3. **Shoulder Shaking:** The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:
 - 0 Normal
 - 1 Slight stiffness and resistance
 - 2 Moderate stiffness and resistance
 - 3 Marked rigidity with difficulty in passive movement
 - 4 Extreme stiffness and rigidity with almost a frozen shoulder
4. **Elbow Rigidity:** The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted separately.)
 - 0 Normal
 - 1 Slight stiffness and resistance
 - 2 Moderate stiffness and resistance
 - 3 Marked rigidity with difficulty in passive movement
 - 4 Extreme stiffness and rigidity with almost a frozen elbow
5. **Wrist Rigidity or Fixation of Position:** The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension, flexion and ulnar and radial deviation:
 - 0 Normal
 - 1 Slight stiffness and resistance
 - 2 Moderate stiffness and resistance
 - 3 Marked rigidity with difficulty in passive movement
 - 4 Extreme stiffness and rigidity with almost frozen wrist
6. **Leg Pendulousness:** The patient sits on a table with his legs hanging down and swinging free. The ankle is grasped by the examiner and raised until the knee is partially extended. It is then allowed to fall. The resistance to falling and the lack of swinging form the basis for the score on this item:
 - 0 The legs swing freely
 - 1 Slight diminution in the swing of the legs
 - 2 Moderate resistance to swing
 - 3 Marked resistance and damping of swing
 - 4 Complete absence of swing
7. **Head Dropping:** The patient lies on a well-padded examining table and his head is raised by the examiner's hand. The hand is then withdrawn and the head allowed to drop. In the normal subject the head will fall upon the table. The movement is delayed in extrapyramidal system disorder, and in extreme parkinsonism it is absent. The neck muscles are rigid and the head does not reach the examining table. Scoring is as follows:
 - 0 The head falls completely with a good thump as it hits the table
 - 1 Slight slowing in fall, mainly noted by lack of slap as head meets the table
 - 2 Moderate slowing in the fall quite noticeable to the eye
 - 3 Head falls stiffly and slowly
 - 4 Head does not reach the examining table
8. **Glabella Tap:** Subject is told to open eyes wide and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted:
 - 0 0-5 blinks
 - 1 6-10 blinks
 - 2 11-15 blinks
 - 3 16-20 blinks
 - 4 21 and more blinks
9. **Tremor:** Patient is observed walking into examining room and is then reexamined for this item:
 - 0 Normal
 - 1 Mild finger tremor, obvious to sight and touch
 - 2 Tremor of hand or arm occurring spasmodically
 - 3 Persistent tremor of one or more limbs
 - 4 Whole body tremor
10. **Salivation:** Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:
 - 0 Normal
 - 1 Excess salivation to the extent that pooling takes place if the mouth is open and the tongue raised
 - 2 When excess salivation is present and might occasionally result in difficulty speaking
 - 3 Speaking with difficulty because of excess salivation
 - 4 Frank drooling

Citation: Simpson GM, Angus JWS: A rating scale for extrapyramidal side effects. *Acta Psychiatrica Scandinavica* 212:11-19,1970

APPENDIX -VII



Name: _____

Date: _____

Barnes Akathisia Rating Scale (BARS)

Instructions: Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

Objective

- 0 Normal, occasional fidgety movements of the limbs
- 1 Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg while sitting, *and/or* rocking from foot to foot or "walking on the spot" when standing, but movements present for less than half the time observed
- 2 Observed phenomena, as described in (1) above, which are present for at least half the observation period
- 3 Patient is constantly engaged in characteristic restless movements, *and/or* has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective

Awareness of restlessness

- 0 Absence of inner restlessness
- 1 Non-specific sense of inner restlessness
- 2 The patient is aware of an inability to keep the legs still, or a desire to move the legs, *and/or* complains of inner restlessness aggravated specifically by being required to stand still
- 3 Awareness of intense compulsion to move most of the time *and/or* reports strong desire to walk or pace most of the time

Distress related to restlessness

- 0 No distress
- 1 Mild
- 2 Moderate
- 3 Severe

Global Clinical Assessment of Akathisia

- 0 *Absent.* No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia
- 1 *Questionable.* Non-specific inner tension and fidgety movements
- 2 *Mild akathisia.* Awareness of restlessness in the legs *and/or* inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress.
- 3 *Moderate akathisia.* Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing
- 4 *Marked akathisia.* Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing.
- 5 *Severe akathisia.* The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia.

Scoring the Barnes Akathisia Rating Scale (BARS)

The Barnes Akathisia Rating Scale is scored as follows:

Objective Akathisia, Subjective Awareness of Restlessness and Subjective Distress Related to Restlessness are rated on a 4-point scale from 0 – 3 and are summed yielding a total score ranging from 0 to 9.

The Global Clinical Assessment of Akathisia uses a 5-point scale ranging from 0 – 4.

Citation: Barnes TR: A Rating Scale for Drug-Induced Akathisia. *British Journal of Psychiatry* 154:672-676, 1989.

APPENDIX - VIII



Arizona Sexual Experiences Scale (ASEX)

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For each item, please indicate your **OVERALL** level during the **PAST WEEK**, including **TODAY**.

1. How strong is your sex drive?

1	2	3	4	5	6
extremely strong	very strong	somewhat strong	somewhat weak	very weak	no sex drive

2. How are you sexually aroused (turned on)?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never aroused

FOR MALE ONLY

3. Can you easily get and keep an erection?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never

FOR FEMALE ONLY

3. How easily does your vagina become moist or wet during sex?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never

If you have had any sexual activity in the past week, please also answer the following two questions. If not, leave questions 4, and 5 blank.

No Sexual activity in past week

4. How easily can you reach an orgasm?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never reach orgasm

5. Are your orgasms satisfying?

1	2	3	4	5	6
extremely satisfying	very satisfying	somewhat satisfying	somewhat unsatisfying	very unsatisfying	can't reach orgasm

COMMENTS:

APPENDIX -IX



