1.1 INTRODUCTION

Schizophrenia is a chronic, severe and disabling brain disorder of heterogenous nature, affecting approximately 1% of the world population. Symptoms of the illness are highly variable from person to person but typically include "positive" symptoms (delusions, hallucinations, thought disorganization), "negative" symptoms (blunted affect, social dysfunction, lack of motivation), cognitive impairments, and mood disturbance. Recurrence of active psychosis, progression of symptoms, and deterioration in all areas of life function are the rule. Schizophrenia inflicts incalculable suffering on patients and their families, and imposes a substantial economic burden on society. (Jibson MD, Glick ID and Tandon R, 2004; Riedel M et al., 2005; Sadock BJ and Sadock VA, 2010)

Outcome in schizophrenia is multidimensional and thus consists of clinical, humanitarian, rehabilitative and cost domains. Accordingly, recovery is conceptualized as the ability to function in the community, socially and vocationally, as well as being relatively free of disease-related psychopathology (Hofer A et al., 2006). Because schizophrenia is a chronic illness, the treatment planning has three goals: 1) reduce or eliminate symptoms, 2) maximize quality of life and adaptive functioning, and 3) promote and maintain recovery from the debilitating effects of illness to the maximum extent possible. Expert consensus guidelines for the treatment of schizophrenia have identified psychosocial interventions and continuous antipsychotic or neuroleptic medications as core treatment modalities (Ascher-Svanum H et al., 2006a).

One of the problems in psychopharmacology is related to the efficacy of the available antipsychotic agents to treat a broad range of schizophrenic symptoms. The second major problem in long-term treatment of schizophrenia is noncompliance and consequently the greater risk of relapse (Fenton WS et al., 1997). Though an individualized approach is reasonable to address the specific reason for medication non-compliance, a growing number of studies have identified two major determinants: the quality of the doctor-patient relationship and the impact of antipsychotic drugs on subjective wellbeing (Van Putten T et al., 1981; Awad AG, 1993; Naber D 1995). So, patients with schizophrenia and their physicians face a number of challenges, such as long-term control of symptoms, maintaining cognitive function and subjective well-being, and preventing relapse. Differences between typical and atypical antipsychotics have been extensively studied and are the topic of ongoing debate whether some atypical antipsychotics are more effective than others and whether atypicals are more effective than typical antipsychotics. (Gorwood P, 2006)

Although conventional antipsychotics are useful for the treatment of schizophrenia, in addition to motor symptoms, they can cause significant adverse effects on drive, emotion and cognition, which are reflected in patients complaining of a reduced quality of life, although may not be detected by objective examination (Karow A and Naber D, 2002; Cohn TA and Sernyak MJ, 2006). A patient's experience of an antipsychotic is important, because unpleasant or dysphoric responses can impair
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therapeutic relationships, lead to medication non-adherence, and have direct negative effects on a patient's quality of life. This negative subjective response might be caused by the inhibition of dopaminergic reward systems, either not induced, or induced to a lesser extent by atypical neuroleptics. There is strong evidence linking neuroleptic-induced dysphoria to non-compliance and to less favourable therapeutic outcome, such as reduced quality of life, and several investigators have emphasised the difficulty in distinguishing symptoms of schizophrenia from side effects of typical antipsychotic drugs. (Naber D and Karow A, 2001, Karow A and Naber D, 2002)

The introduction of atypical or second generation antipsychotics (SGAs) broadened the criteria for effective antipsychotic treatment to include the subjective assessment of improvement in patients' quality of life. The improvement of negative, affective and cognitive symptoms, and particularly the better subjective well-being as well as quality of life are major advantages for the new antipsychotic drugs. The focus of treatment with novel antipsychotics is thus no longer only symptom reduction alone, but improvement of quality of life. Novel antipsychotics may also increase patients' ability to participate in psychosocial rehabilitation, of major relevance to reduce negative symptoms a crucial barrier towards a better quality of life. (Karow A and Naber D, 2002)

The patient's perspective as an important feature of quality of life measurement has been neglected for long time. Subjective complaints of schizophrenic patients on antipsychotics need to be taken seriously by clinicians and researchers. Quality of life (QOL) assessment is a new methodological approach to differentiate therapeutic effects and to give more consideration to the patient's perspective. The previous lack of interest in this domain may have been due to the inability to improve it with conventional agents, the misconception that schizophrenic patients were unable to subjectively evaluate their quality of life (Naber D and Karow A, 2001; Karow A and Naber D, 2002) and the belief that such data are not necessary because the psychiatrists' perspective, "objective" psychopathology includes these domains (Cohn TA and Semyak MJ, 2006). However, numerous trials demonstrated that 63-95% of clinically stable patients can evaluate their well-being, affective state of QOL reliably and with sufficient consistency. The increasing interest in subjective well-being and quality of life of schizophrenic patients represent both a conceptual shift in therapeutic outcome criteria and a biopsychosocial concept of health. While symptom reduction alone was the most essential outcome parameter for a long time, more ambitious success criteria, including the patients' perspective, are now, nearly 50 years after the development of the first neuroleptic drug, finally being considered. (Karow A and Naber D, 2002)

Considering the enormous use of neuroleptics over the last decades, it is surprising that the systematic evaluation of patients' subjective complaints has received little attention. Only a few studies explored the clinical relevance of adverse subjective effects of neuroleptics (antipsychotics). For a long time, the reduction of positive symptoms alone was the most important outcome parameter, but the development of atypical antipsychotic drugs in the early 1990s resulted in the adoption of more wide-reaching measures of therapeutic outcome. A few decades ago, research on
such outcomes as subjective tolerability or quality of life was looked at as soft science, a view reflected in a certain publication bias and low priority in research funding. (Awad AG, 2004a)

However, the assessment of the subjective effects of antipsychotics is of major importance to assess both the benefits and burdens of drug therapy. Particularly during long-term treatment, it is essential to thoroughly consider the patient’s perspective which sometimes markedly differs from that of the psychiatrist (Naber D et al., 2001). Given the clinical significance and impact the outcome of treatment, it is obvious that attempts to determine the utility of new antipsychotics should include measurement of subjective response (Garcia-Cabeza I et al., 2001).

As schizophrenia is a chronic disorder, it is important that treatment be given over a long period of time to avoid relapse. Staying on the drug is critical for successful treatment as compliance is a major problem. There is no single antipsychotic that is best for every schizophrenia patient, as individual responses differ markedly. The heterogeneity of atypical antipsychotics with marked differences in their side effect profile increases the difficulty, but also the probability to select an effective and tolerable drug for the individual patient. A better consideration of the patients’ perspective can improve therapeutic alliance, medication adherence and the long-term prognosis. As schizophrenia is a chronic disorder, it is important that treatment be given over a long period of time to avoid relapse. Staying on the drug is critical for successful treatment as compliance is a major problem. Thus determinants of drug’s ‘effectiveness’ in schizophrenia are not mere efficacy (symptom relief) and tolerability (Lieberman JA et al., 2005) but are also in addition - normal functions’ restoration, relapse prevention and remission maintenance with resultant treatment adherence on long-term treatment. Much research was targeted at developing antipsychotics with improved clinical efficacy and fewer adverse effects. However, patients’ attitudes and values, their concept of illness and health as well as their previous experiences with medication may significantly affect the subjective response to neuroleptics. Furthermore, a better understanding of the relationship between psychopathology, neuroleptic-induced side effects and patients’ quality of life may contribute to more individualised treatment (Karow A and Naber D, 2002). So, the long-term prospective studies of subjective well-being/quality of life of schizophrenic patients receiving antipsychotics in Indian population are called for.

Schizophrenia treatment in the context of clinical trial is often substantially different from daily clinical practice. While randomised, placebo-controlled trials and open-label extensions can provide valuable information about the long-term efficacy and tolerability of newer antipsychotic agents,
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they cannot address all the variables that may affect treatment outcome. Factors such as cognitive function, antipsychotic side effects, patients' attitudes to medication and subjective well being can all affect the results of treatment in real-life clinical practice. In addition, patients themselves may refuse to participate in placebo-controlled studies because of a fear of being under-treated (Gorwood P, 2006). The observational studies are designed to assess the relevance and credibility of clinical trial outcomes in real-life settings. In doing so, they supplement findings from both randomised controlled trials (RCT) and epidemiological studies by allowing us to observe patterns in robust, real-world safety and effectiveness data from a naturalistic setting (Karagianis J et al, 2009). Naturalistic studies provide a unique opportunity to understand the nature of subjective response to antipsychotic treatment that patients with schizophrenia experience in the course of real-world. Noninterventional, naturalistic studies facilitate examination of current clinical practices and provide an understanding of the impact of the biopsychosocial aspects of schizophrenia. (Dossenbach M, 2008)

Patients with schizophrenia are at greater risk of developing obesity, type 2 diabetes, hypertension and dyslipidemia as compared to general population (Jacob R and Chowdhury AN, 2008). The advent of the newer generation or novel or atypical or second generation antipsychotics during the last 15 years represents a significant improvement over the effectiveness of conventional antipsychotics with added usefulness in negative symptoms of schizophrenia and are less likely to cause distressing adverse effects especially extrapyramidal side effects (EPS) found with conventional antipsychotics. However, these agents are not magic bullets and are associated with their own attendant treatment complications (Shahin A, 2006).

Indians in particular, are more prone to develop metabolic side effects such as diabetes mellitus, dyslipidaemias and cardiovascular disease. Important reasons could be their excess body fat and adverse body fat patterning, including abdominal obesity, even when the body mass index is within the currently defined limits (Jacob R, 2009). India is a country with heterogeneous ethnicity and hence the food and other habits differ in different states and regions as well as in urban and rural population. So, looking to the Indian patients with psychotic illness exposed to antipsychotics and especially SGAs, there is a need for further research with focus on this area.

Metabolic side effects of antipsychotic treatment include weight gain, dyslipidemia and increased susceptibility to diabetes. Although it is difficult to separate the contributions of illness, lifestyle, and medication factors to these risks, there is now a pressing clinical need to monitor patients treated with antipsychotic medications for metabolic disturbance (Cohn TA and Sernyak MJ, 2006). A
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Consensus development conference on antipsychotic drugs and obesity and diabetes has recommended the monitoring protocol for patients on SGAs. However, screening for the metabolic conditions does not happen regularly in large psychiatric units and hospitals (Jacob R, 2009).

Looking to the above needs and paucity of literature of long-term research in Indian population, the present study aimed to further examine effectiveness, subjective well-being and tolerability (with focus on metabolic effects) in schizophrenic patients receiving antipsychotic treatment. This 48-weeks long prospective, noninterventional (observational) study was carried out at public hospital’s psychiatry outpatient department which treats patients with various psychiatric disorders belonging to wide and variegated socio-economic-religious background, and dispenses certain psychotropic medicines free of charge to the patients. Among oral atypical antipsychotics risperidone, olanzapine and clozapine are dispensed free of charge. So, in this study those patients diagnosed with schizophrenia and undergoing antipsychotic treatment on the best possible clinical knowledge, judgement and experience of the attending psychiatrist, and who were prescribed antipsychotic monotherapy (risperidone or olanzapine or clozapine) and agreeable for the metabolic (fasting blood glucose and lipid profile) tests were selected for 48-weeks observational follow-up.

1.2. AIMS AND OBJECTIVES

The present 48-weeks long prospective, observational (noninterventional) study aimed to examine effectiveness, subjective well-being and tolerability (with focus on metabolic effects) in schizophrenic out-patients receiving atypical antipsychotic monotherapy (risperidone or olanzapine or clozapine) in a naturalistic treatment setting as in routine clinical practice. The study was carried out with following objectives:

- Assessment of functioning and subjective wellbeing of patients receiving any of the three atypical antipsychotics using GAF (Global Assessment of Functioning) scale and SWN-20 (subjective wellbeing under neuroleptic treatment) scale.

- Assessment of the tolerability (with focus on metabolic effects) of individual study antipsychotic.

- Assessment of efficacy of study antipsychotic in improving psychopathology of schizophrenia during the study using PANSS (Positive and Negative Syndrome Scale) and CGI (Clinical Global Impressions) Scale.

- Time to all-cause medication discontinuation. It was the time until medication discontinuation of study antipsychotics (risperidone or olanzapine or clozapine as monotherapy) in enrolled patients with schizophrenia for any and specific cause.