

Review Article

Schizophrenic Patient Care – Pharmacists Role

Juno J. Joel*

Drug and Poison Information Centre, Department of Pharmacy Practice, NGSM Institute of Pharmaceutical Sciences, Mangalore, Karnataka, India.

***Corresponding author**

Juno J. Joel

Email: junojoel@nitte.edu.in

Abstract: Schizophrenia is a complex psychiatric illness of unsure aetiology, afflicting approximately 1% of the world-wide population. Schizophrenia generally appears between the age of 16 and 30; hence, it becomes a long-standing, chronic disease. Treatment choices are psychosocial and pharmacotherapeutic interventions. Our article represents the role and the need of pharmacists in the area of schizophrenic patient care. The recommendations are to widen the role of pharmacists and to implement it especially in the developing nations. Towards pharmaceutical care the pharmacists should have a vast knowledge in the area of drug therapy management and drug related problems. To initiate, there is a need of good association between pharmacist, psychiatrists and all other mental health care providers. Pharmacists should be kept updated with recent drug related information's by attending regular education and training programmes. Thus, pharmacists can help the physicians, particularly, in the decision making situations. Hence, well trained and competent pharmacists can take an active role in the mental health care management team.

Keywords: Schizophrenia, complications, pharmacist

Introduction

Schizophrenia is a multipart psychiatric disorder which has mystified physicians, philosophers, and general public for years. According to the world (Mental) health report 2001, about 24 million people worldwide suffer from schizophrenia. The prevalence of schizophrenia is about 0.5-1% [1]. Schizophrenia incidence is equal in men and women [2] and the occurrence of the first episode appears usually during the adolescence [3]. The diagnosis of schizophrenia cannot be made or monitored by laboratory or physical tests, the physician must use target symptoms obtained from a patient interview and previous records to access the treatment response [4]. Drugs, Psychotherapy and social interventions together form the management of schizophrenia. Most patients are managed by a blend of family or community care with infrequent hospital admission, supported by antipsychotic drug therapy. Nowadays, few schizophrenic patients need lasting institutional care. The intention in managing schizophrenia are to, control acute attacks and prevent self-harm or harming others, attend to social and familial factors, rehabilitate the patient if possible and start long-term support and maintenance therapy. Patients with chronic disease conditions need continuation therapy, either to suppress their symptoms or to prevent relapses. The management of such patients has undergone a wide range of alterations in recent past [5]. This article gives detailed information on the role of

the pharmacist and his involvement in the mental patient care.

Pharmaceutical Care

Pharmaceutical care is the responsible condition of drug therapy for the purpose of achieving specific outcomes that improve a patient's quality of life. These outcomes are

- treat a disease;
- eradication or reduction of a patient's symptom
- slowing of a disease progression
- preventing a disease or symptom.

Pharmaceutical care involves the progression through which a pharmacist cooperates with a patient and other professionals in designing, implementing, and monitoring a therapeutic procedure that will produce explicit therapeutic outcomes for the patient. This in turn involves three major functions:

- identifying potential and actual drug-related problems;
- resolving actual drug-related problems; and
- preventing drug-related problems.

Pharmaceutical care is a necessary aspect of health care and should be incorporated with other elements. Pharmaceutical care is, however, provided for the direct benefit of the patient, and the pharmacist is accountable directly to the patient for the quality of that care. The

essential relationship in pharmaceutical care is a reciprocally beneficial exchange in which the patient grants rights to the provider, and the provider gives competence and obligation to the patient. The fundamental goals, processes, and relationships of pharmaceutical care exist apart from practice settings [6].

Complications in Schizophrenic Patients

1. Non-adherence to Medications

Antipsychotic medications represent the keystone of pharmacological management for patients with schizophrenia. Although these agents have been shown to recover psychopathology, reducing relapse and improved performing non-adherence to treatment with antipsychotics is common. Non-adherence rates array from 20% to 89%, with an average rate of about 50%, have been described [7-9]. Among schizophrenic patients, non-adherence to treatment with antipsychotic medication is associated with a high number of clinical visits and more psychiatric hospitalizations [10-12]. Improving adherence to treatment with antipsychotic medication in patients with psychotic disorders is a difficult task [13-14]. Finding the risk factors connected with medication non-adherence is the preliminary step because adjustable risk factors might become targets for future interventions.

2. Adverse effects of antipsychotics used in Schizophrenic patients

a. Sedation

Sedation is common among antipsychotic drugs and is dose related. It can be a cause of poor compliance and, if continual, can interfere with social and occupational functioning. Several patients become tolerant to the sedative effect in due course. Low-potency FGAs and clozapine are more sedating, with some effect from olanzapine and quetiapine [15]. Somnolence can be improved by lowering the dosage, shifting to a single bed time dose, or changing to a less sedating medication.

b. Hypotension

Incidence of orthostatic hypotension can occur depends on the degree of $\alpha 1$ -adrenoreceptor antagonism, particularly with low-potency FGAs and clozapine. It may also occur with risperidone and quetiapine, especially with quick titration. This effect is more common in elderly patients with risk of falls, those on hypertension medications, and those who have other cardiovascular disorders. With cautious dose titration, patients may become tolerant to this effect. Treatment choice includes decreasing or dividing doses or switching to a drug with a lesser anti-adrenergic effect [15].

c. Anticholinergic Effects

The effect of anticholinergics include, constipation, urinary retention, dry mouth, blurring of vision and occasionally, cognitive impairment. These

symptoms may lead to additional problems such as tooth decay, falls, or gastrointestinal difficulties. Low-potency FGAs and clozapine are highly possible to cause anticholinergic effects; olanzapine and quetiapine have been shown to elicit the same at high dosages [16]. Once needed, doses can be lowered or divided to help in improving this difficulty.

d. Extrapyramidal Symptoms

Four main extrapyramidal symptoms by antipsychotic medications: pseudoparkinsonism, akathisia, acute dystonia, and tardive dyskinesia. The first three usually begin within a few weeks of initiating a fresh medication (or dose titration). These symptoms may cause uneasiness, social stigma, and poor compliance. They are more expected to occur with higher dosages of high-potency FGAs, such as haloperidol, and are less likely with FGAs that have weaker dopamine blockade. Quite a few meta-analyses, most comparing SGAs with haloperidol, have revealed that SGAs are less possible to cause extrapyramidal symptoms [15]. However, recent researches comparing SGAs with low potency FGAs have not shown this variation [17-19].

e. Pseudoparkinsonism

It is a reversible syndrome that includes tremulousness in the hands and arms, rigidity in the arms and shoulders, bradykinesia, akinesia, hypersalivation, masked facies, and shuffling gait. The presence of bradykinesia or akinesia can create an investigative dilemma, with symptoms similar to depression or even the negative symptoms of schizophrenia (i.e., an inability to pay attention, the loss of a sense of pleasure, the loss of will or drive, disorganization or poverty of thoughts and speech, flattening of affect, and social withdrawal). Management options include reduction in dosage or the addition of anticholinergic agents.

f. Akathisia

Akathisia is illustrated as a feeling of internal restlessness that can be manifested as excessive pacing or incapability to remain motionless for any length of time. It is hard to differentiate akathisia from psychiatric anxiety and agitation. Treatment can include a reduction in dosage when feasible, or the addition of a beta blocker in low doses, such as propranolol at 20 to 80 mg per day [20].

g. Dystonia

These reactions are spastic contractions of the muscles, together with oculogyric crisis, retrocollis, torticollis, trismus, opisthotonos, or laryngospasm. These reactions can be life threatening if gone untreated. Management often requires treatment with intravenous or intramuscular anticholinergic agents.

h. Hyperprolactinemia

Antipsychotic drug can cause high prolactin levels by stopping the normal tonic inhibition on pituitary mammatropic cells of dopamine, which is produced in the hypothalamus. Hyperprolactinemia is common with the use of any FGA, as well as with the SGA risperidone (60% in women and 40% in men), [21] and is dose related. Though it appears to be less frequent with other SGAs, use of olanzapine and ziprasidone at high dosages has also reported very similarly [15]. Hyperprolactinemia can be asymptomatic, but can cause gynecomastia, galactorrhea, amenorrhea, sexual dysfunction, acne, hirsutism, infertility, and loss of bone mineral density. Symptoms frequently emerge within a few weeks of commencement of antipsychotic or increasing the dosage, but can also occur after long-term constant use. There is increasing facts that chronic hyperprolactinemia from antipsychotics can cause osteoporosis and an increased risk of hip fracture. A case-control analysis of a large general practice database in the United Kingdom illustrate that the risk of hip fracture was 2.6 times higher in patients taking prolactin-raising antipsychotics compared with the general population[22]. Incidence of osteoporosis, sexual side effects, or prolactin dependent breast cancer may require switching to an antipsychotic that does not elevate prolactin levels, such as aripiprazole or quetiapine [23].

i. Sexual Dysfunction

Around 43 percent of patients who were on antipsychotic medications report problems with sexual dysfunction, a adverse effect that can lead to reduced medication adherence [24]. Antipsychotic usage have influence in different phases of sexual function, including libido, arousal, and orgasm.

Both FGAs and SGAs can weaken arousal and orgasm in both males and females [25-26]. Especially FGAs have been found to cause erectile and ejaculatory dysfunction including painful, retrograde ejaculation, as well as priapism.

j. Agranulocytosis

Clozapine may cause neutropenia rarely (Absolute Neutrophil Count [ANC] of less than 1,500 cells per mm³ [1.50×10^9 per L]) and agranulocytosis (ANC of less than 500 cells per mm³ [0.50×10^9 per L]) that can lead to potentially serious infections. It may occur in less than 1 percent of patients, almost always within three months of starting treatment [27]. Risk increases with older age, female sex, and Asian race¹⁵.

k. Cardiac Arrhythmias

Antipsychotics can prolong ventricular repolarization (prolonged QT interval), which can in turn lead to torsades de pointes and sudden cardiac death. This effect is noticeable with the low-potency FGA (Thioridazine) and the SGA (Ziprasidone), and is dose dependent [28]. The occurrence of sudden cardiac

death in patients who receive antipsychotics is about twice that of the general population [29-30]. Physicians have to avoid using combined antipsychotic medications with other medications that prolong the corrected QT interval (e.g., classes I and III antiarrhythmic drugs, tricyclic antidepressants, some antibiotics). It may be cautious to check baseline or post treatment electrocardiography, especially with higher risk patients. There is no proof of effectiveness by doing so [31].

l. Seizures

Antipsychotics should be used with caution in patients who have a history of seizures and in those with organic brain disorders. Commonly, the antipsychotic with more sedating properties lowers the seizure threshold. Seizures are common with low-potency FGAs and clozapine, especially at high doses [32].

m. Metabolic Issues

One of the common adverse effects of using antipsychotic medications is weight gain, and it is difficult to control [33]. The outcome is worse with clozapine and olanzapine; less with aripiprazole and ziprasidone; and intermediate with other antipsychotics that include low-potency FGAs [34]. Antipsychotic medications can lead to a wide range of abnormalities in, glycemic control from insulin resistance to diabetic ketoacidosis [35]. The extent of risk is difficult to enumerate because of the presence of other diabetes risk factors in the population. But the weight gain associated with antipsychotics obviously contributes; there appear to be other independent effects additionally [36-37]. Several antipsychotic medications is also associated with dyslipidemia. Low-potency FGAs and the SGAs clozapine, olanzapine, and quetiapine are also associated with a higher risk of hyperlipidemia [38-41].

3. Elderly Patients

Antipsychotic medications are used in elderly patients who have dementia-related psychosis or other behavioral difficulty. In April 2005, the FDA issued a boxed warning for SGAs after a meta-analysis showed an increased risk of death associated with their use in the study population [42]. In June 2008, two large cohort studies showed similar risk with FGAs, boxed warnings were added to this class additionally [43-44].

4. Drug Abuse and Addiction

Schizophrenic patients are more likely to misuse a variety of substances than other healthy individuals. There is substantial evidence that schizophrenia patients have higher than average rates of alcohol and illicit drug use, cigarette smoking, and polydipsia. Comorbid substance abuse and dependence have significant effects on the course of illness, on physical health, on hospitalization, and on quality of life [45]. Cigarette smoking in higher rates are found in schizophrenic patients than in normal subjects and in

patients with other psychiatric disorders [46]. Smoking increases drug metabolism and consequently may be associated with the use of higher neuroleptic doses [47]. It has been thought that nicotine increases the release of dopamine in some areas of the brain [48]. Comorbid alcohol abuse or dependence was found to be associated with an increased incidence of TD (Tardive dyskinesia) [49], heavy alcohol use may result in a “premature aging” of the brain, thereby increasing the risk for TD. Studies have been carried out to address the effect of multiple substance use in schizophrenia. It was noticed that substance interactions may further compromise health status, cognitive functioning and psychiatric symptoms [50].

5. Suicidal intentions in Schizophrenia

Schizophrenia patients with substance abuse may be more likely to act on suicidal ideas [51]. Hence, suitable assessment and treatment of substance use disorders in schizophrenia is vital. Some of the common reasons for suicide in schizophrenia can include the presence of co-morbid depressive symptoms, command hallucinations commanding the patient to commit suicide, impulsive behavior and presence of anhedonia. It is necessary to be alert of possibility of suicide while treating a patient with schizophrenia [52].

Pharmacist’s role in mental health care

Pharmacists in mental health care have been involved in several collaborative services with physicians, including (1) monitoring drug therapy and reducing side effects, (2) assessing drug serum concentrations, (3) identifying drug interactions, (4) assisting in the development of treatment plans, and (5) identifying ways to improve medication adherence. For the past three decades these kinds of collaborative services to individuals with mental illness have shown to have a significant and positive impact on several patient and health system outcomes [53-57]. Community pharmacists have also been shown to have a considerable and positive impact on psychotropic education and monitoring [58].

As one of the most accessible health care professionals, pharmacists can positively impact patient outcomes by stressing the importance of medication adherence, as well as encouraging patients to maintain regular visits with their primary health care provider. When counselling patients, pharmacists should remind them about the benefits of medication therapy and educate them regarding the potential adverse effects of the selected medication.

Patients should be reminded not to discontinue any of their medication unless directed by their physician, report any side effects to their primary health care provider, and not to use any other medications, including non-prescription drugs, vitamins, and herbal medications, without seeking advice from their primary health care provider. It also is important for patients to

be advised against the use of alcohol. Because quitting smoking may be difficult for patients with schizophrenia, smoking cessation strategies such as nicotine replacement methods may be recommended.

Successful therapy starts when patients have a thorough understanding of their therapy and the importance of therapy adherence. Pharmacists can be instrumental in identifying possible contraindications or drug interactions for this patient population and recommending various strategies that patients can use to increase adherence to their therapy, such as the use of medication reminder devices, using automated-refill features to ensure prescriptions are filled on time, and using one pharmacy for all prescriptions. Most importantly, pharmacists can assist patients with schizophrenia by showing empathy, providing encouragement and support, and reminding them that adhering to their therapy is the most effective tool in managing schizophrenia [59-60].

Educating the Patient and Family

Noncompliance is a problem with some patients once they are discharged from the hospital. It is important for the pharmacist to accurately evaluate the patient’s ability to assume responsibility for taking drugs at home. The administration of antipsychotic drugs becomes a family responsibility if the outpatient appears to be unable to manage his or her own drug therapy. The pharmacist explains any adverse reactions that may occur with a specific antipsychotic drug and encourages the patient or family members to contact the primary health care provider immediately if a serious drug reaction occurs. The pharmacist can advise the patient or family member. It includes the following points:

- Take regular clinical appointments when necessary because close monitoring of therapy is essential.
- Report any unusual changes or physical effects to the primary health care provider.
- Take the drug exactly as directed. Do not increase, decrease, or omit a dose or discontinue use of this drug unless directed by the physician.
- Do not drive or perform other hazardous tasks if drowsiness occurs.
- Do not take any non-prescription drug unless use of a specific drug has been approved by the physician.
- Inform physicians, dentists, and other medical personnel about the present antipsychotic drug therapy during consultations on other medical reasons.
- Never use alcoholic beverages, cigarette or any other illicit drugs.
- If dizziness occurs when changing position, rise slowly when getting up from the bed or a chair. If dizziness is severe, always take somebody’s help.

- If dryness of the mouth occurs, relieve it by taking frequent sips of water, chew a hard candy, or chewing gum (preferably sugarless).
- Inform your primary care provider if you become pregnant or intend to become pregnant during drug therapy [60].

Conclusion

The mental health system is still considered by many to be quite fragmented, leaving mentally ill patients with critical gaps on care. Current and future pharmacists should view themselves as a part of an interdisciplinary solution that resolves these gaps by helping to provide continuity in medication related services and maximizing pharmacotherapy outcomes that facilitate the fast recovery of individuals with mental illness.

REFERENCES

1. Niraj Ahuja; A Short Textbook of Psychiatry, Seventh edition, Jaypee Brothers Medical Publishers, 2011: 54-55
2. Howes OD, Egerton A, Allan V; Mechanisms Underlying Psychosis and Antipsychotic Treatment Response in Schizophrenia: Insights from PET and SPECT Imaging. *Curr Pharm Des*, 2009;15(22):2550-2559.
3. Cullen KR, Kumra S, Regan J; Atypical Antipsychotics for Treatment of Schizophrenia Spectrum Disorders. *Psychiatric Times*, 2008;25(3). 2008.
4. Rene A; Schizophrenia” Applied therapeutics the clinical use of drugs, Pennsylvania: Lippincott Williams & Wilkins, 2009; 78-9.
5. Russell J and Norman D. “Schizophrenia” Pathology and Therapeutics for Pharmacists, India: Pharmaceutical Press, 2008; 413-423.
6. Helper DD, Strand LM; Opportunities and Responsibilities in Pharmaceutical Care, *Am.J. Pharm. Educ.*, 1989; 53, 7S-15S.
7. Fenton WS, Blyler CR, Heinssen RK; Determinants of medication compliance in schizophrenia: empirical and clinical findings. *Schizophr Bull*, 1997; 23:637-651
8. Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV; Prevalence of and risk factors for medication non-adherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry*, 2002; 63:892-909
9. Young JL, Zonana HV, Shepler L; Medication noncompliance in schizophrenia: codification and update. *Bull Am Acad Psychiatry Law*, 1986; 14:105-122
10. Weiden PJ, Olfson M; Cost of relapse in schizophrenia. *Schizophr Bull*, 1995; 21:419-429
11. Valenstein M, Copeland LA, Blow FC, McCarthy JF, ZeberJE, Gillon L, Bingham CR, Stavenger T; Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. *Med Care*, 2002; 40:630-639
12. Terkelsen KG, Menikoff A; Measuring the costs of schizophrenia: implications for the post-institutional era in the US. *Pharmacoeconomics*, 1995; 8:199-222
13. Zygmunt A, Olfson M, Boyer CA, Mechanic D; Interventions to improve medication adherence in schizophrenia. *Am J Psychiatry*, 2002; 159:1653-1664
14. McDonald HP, Garg AX, Haynes RB; Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA*, 2002; 288:2868-2879.
15. Haddad PM, Sharma SG; Adverse effects of atypical antipsychotics: differential risk and clinical implications. *CNS Drugs*, 2007;21(11):911-936.
16. Chew ML, Mulsant BH, Pollock BG; A model of anticholinergic activity of atypical antipsychotic medications. *Schizophr Res*, 2006; 88(1-3):63-72.
17. Lieberman JA, Stroup TS, McEvoy JP; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209-1223.
18. Jones PB, Barnes TR, Davies L; Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry*, 2006;63(10):1079-1087.
19. Leucht S, Wahlbeck K, Hamann J, Kissling W; New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. *Lancet*, 2003;361(9369):1581-1589.
20. Kramer MS, Gorkin R, DiJohnson C; Treatment of neuroleptic-induced akathisia with propranolol: a controlled replication study. *Hillside J Clin Psychiatry*, 1989;11(2):107-119.
21. Kleinberg DL, Davis JM, de Coster R, Van Baelen B, Brecher M; Prolactin levels and adverse events in patients treated with risperidone. *J Clin Psychopharmacol*, 1999;19(1):57-61.
22. Howard L, Kirkwood G, Leese M; Risk of hip fracture in patients with a history of schizophrenia. *Br J Psychiatry*, 2007;190:129-134.
23. Haddad PM, Wieck A; Antipsychotic-induced hyperprolactinaemia. *Drugs*, 2004; 64(20):2291-2314.

24. Wallace M; Real progress—the patient’s perspective. *Int Clin Psychopharmacol*. 2001;16(suppl 1):S21-S24.
25. Ghadirian AM, Chouinard G, Annable L; Sexual dysfunction and plasma prolactin levels in neuroleptic-treated schizophrenic outpatients. *J Nerv Ment Dis*, 1982;170(8):463-467.
26. Wirshing DA, Pierre JM, Marder SR, Saunders CS, Wirshing WC; Sexual side effects of novel antipsychotic medications. *Schizophr Res*, 2002;56(1-2):25-30.
27. Alvir JM, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA; Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. *N Engl J Med*, 1993;329(3):162-167.
28. Kutcher S, Brooks SJ, Gardner DM; Expert Canadian consensus suggestions on the rational, clinical use of ziprasidone in the treatment of schizophrenia and related psychotic disorders. *Neuropsychiatr Dis Treat*, 2005;1(2):89-108.
29. Glassman AH, Bigger JT Jr; Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry*, 2001; 158(11):1774-1782.
30. Ray WA, Chung CP, Murray KT, Hall K, Stein CM; Atypical antipsychotic drugs and the risk of sudden cardiac death [published correction appears in *N Engl J Med*, 2009;361(18):1814
31. Roden DM; Drug-induced prolongation of the QT interval. *N Engl J Med*, 2004;350(10):1013-1022.
32. Pacia SV, Devinsky O; Clozapine-related seizures: experience with 5,629 patients. *Neurology*. 1994;44(12):2247-2249.
33. Bryden KE, Kopala LC; Body mass index increase of 58% associated with olanzapine. *Am J Psychiatry*. 1999;156(11):1835-1836.
34. Gardner DM, Baldessarini RJ, Waraich P. Modern antipsychotic drugs: a critical overview. *CMAJ*. 2005;172(13):1703-1711.
35. Ramaswamy K, Kozma CM, Nasrallah H; Risk of diabetic ketoacidosis after exposure to risperidone or olanzapine. *Drug Saf.*, 2007;30(7):589-599.
36. Howes OD, Bhatnagar A, Gaughran FP, Amiel SA, Murray RM, Pilowsky LS; A prospective study of impairment in glucose control caused by clozapine without changes in insulin resistance. *Am J Psychiatry*, 2004;161(2):361-363.
37. Newcomer JW, Haupt DW, Fucetola R; Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Arch Gen Psychiatry*, 2002;59(4):337-345.
38. Koro CE, Meyer JM; Atypical antipsychotic therapy and hyperlipidemia: a review. *Essent Psychopharmacol*. 2005;6(3):148-157.
39. Melkersson K, Dahl ML; Adverse metabolic effects associated with atypical antipsychotics. *Drugs*. 2004;64(7):701-723.
40. Meyer JM, Koro CE; The effects of antipsychotic therapy on serum lipids: a comprehensive review. *Schizophr Res*. 2004;70(1):1-17.
41. Newcomer JW; Metabolic considerations in the use of antipsychotic medications. *J Clin Psychiatry*. 2007;68(suppl 1):20-27.
42. Schneider LS, Dagerman KS, Insel P; Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA*. 2005;294(15):1934-1943.
43. Gill SS, Rochon PA, Herrmann N; Atypical antipsychotic drugs and risk of ischaemic stroke. *BMJ*. 2005;330(7489):445.
44. Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, Wang PS; Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *CMAJ*. 2007;176(5):627-632.
45. Mueser KT, Bellack AS, Blanchard JJ; Comorbidity of schizophrenia and substance abuse: Implications for treatment. *Journal of Consulting and Clinical Psychology* 1992; 60:845-856.
46. Hughes JR, Hatsukami DK, Mitchell JE, Dahlgren LA; Prevalence of smoking among psychiatric outpatients. *American Journal of Psychiatry*, 1986; 143:993-997.
47. Goff DC, Henderson DC, Amico E; Cigarette smoking in schizophrenia: Relationship to psychopathology and medication side effects. *American Journal of psychiatry*, 1992;149:1189-1194.
48. Giorguieff-Chesselet MF, Kernel ML, Wandscheer D, Glowinski J; Regulation of dopamine release by presynaptic nicotine receptors on rat striatal slices: Effect of nicotine in a low concentration. *Life Sciences*, 1979; 25:1257-1262.
49. Jeste DV, Harris MJ, Krull A, Kuck J, McAdams LA, Heaton RK; Clinical and neuropsychological characteristics of patients with late-onset schizophrenia. *American journal of Psychiatry*, 1995; 152:722-730.
50. Koczapski AB, Ledwidge B, Paredes J, Kogan C, Higenbottam J; Multisubstance intoxication among schizophrenic inpatients: Reply to Hyde. *Schizophrenia Bulletin*, 1990; 16(3):373-375.
51. Cohen LJ, Test MA, Brown RL; Suicide and schizophrenia: Data from a prospective community treatment study. *American Journal of Psychiatry*, 1990; 147:602-607.

52. Niraj A; A Short textbook of psychiatry, 7th ed, Jaypee brothers medical publishers, Harayana, 2011:57
53. Bond CA, Salinger RJ; Fluphenazine outpatient clinics: a pharmacists role. *J J Clin Psych*, 1979;40:501-3.
54. Saklad SR, Ereshefsky L, Jann MW, Crismon ML; Clinical pharmacists impact on prescribing in an acute adult psychiatric facility. *Drug Intell Clin Pharm*, 1984;18:632-4.
55. Lobeck F, Traxler WT, Bobiner DD;The cost-effectiveness of a clinical pharmacy services in an outpatient mental health clinic. *Hosp Community Pharm*, 1989;40(6):643-5.
56. Finley PR, Rens HR, Pont JT; Impact of a collaborative pharmacy practice model on the treatment of depression in primary care. *Am J Health Syst Pharm*, 2002;59:1518-26.
57. Finley PR, Crismon ML, Rush AJ; Evaluating the impact of pharmacists in mental health; a systemic review. *Pharmacotherapy*, 2003;23(12):1634-44.
58. Bultman DC, Svarstad BL; Effects of pharmacist monitoring on patient satisfaction with anti-depressant medication therapy. *J Am Pharm Assoc*, 2002;42:36-43.
59. Rickles NM, Savarstad BL, Statz-Paynter J, Taylor LV, Kobak K; Pharmacists' telemonitoring of antidepressant use: effects on patient feedback and other outcomes. *J Am Pharm Assoc*, 2005;45(3):344-53.
60. Rickles NM Savarstad BL, Statz-Paynter J, Taylor LV, Kobak K; Improving patient feedback regarding antidepressant treatment: an experiment in eight community pharmacies. *J Am Pharm Assoc*, 2006;46(1):25-32.