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ADRS DUE TO ANTIPSYCHOTIC DRUGS: A REVIEW

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INTRODUCTION

WHO defines an ADR as "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function".[1] The antipsychotic drugs are chemically diverse but have the common property of alleviating the symptoms of organic as well as functional psychosis.[2] Antipsychotics are among the most effective drugs used in psychiatry in the maintenance therapy of schizophrenia, mania, or in acute psychotic reactions.[3] These drugs are also capable of causing a wide range of potential adverse drug reactions that can lead to non-compliance that can impair quality of life, may cause stigma and physical morbidity which may lead to discontinuation of medication and in extreme cases may be fatal.[4]

Antipsychotic drugs have a high therapeutic index and are generally safe agents. Adverse effects are extensions of many pharmacological actions of these drugs which include those on the cardiovascular, central, autonomic nervous system and endocrine systems.[4,5-7] The knowledge of how the prevalence and severity of adverse effects vary for different antipsychotics allows the clinicians to choose the safer and effective drug therapy for the patients.[8] Atypical antipsychotics differ from conventional agents as atypical antipsychotics have lower risk of extrapyrimidal side effects and also significantly reduce both positive as well as negative symptoms of shizophrernia.[9] Besides having lower risk of extrapyrimidal side effects, atypical antipsychotic agents present their own spectrum of adverse effects that include hypotension, seizures, weight gain, increased risk of diabetes mellitus and hyperlipidemia.[9-11] These ADRs in hospitalized psychiatric patients are not only common, but they also have high rate of preventability. To identify medications that should be targeted for quality improvement projects and patient education, a healthcare system can use data on

frequency, severity, probability and preventability. Targeting high-risk medications that have been identified through analysis may have a significant impact on reducing preventable ADRs.[12]

The aim of this review is to present an updated analysis of ADRs associated with the use of antipsychotic drugs in different populations with psychiatric disorders and how to manage ADRs in general perspective and what are the future developments in the management of adverse drug reactions.

Mechanism of antipsychotic action

Pharmacodynamics property of all antipsychotics in the brain is D_2 receptors antagonism that has given rise to the hypothesis that schizophrenia and other related disorders involves the dysregulation of dopaminergic circuits with excess dopaminergic activity in mesolimbic pathway which lead to the positive symptoms of psychosis and reduced dopaminergic signaling in the mesocortical pathways leads to the negative symptoms. The evidence for the dopamine hypothesis comes from not only the efficacy of D_2 receptor antagonism, but also through the effect of D_2 agonists such as amphetamine in precipitating psychosis and the effect of dopamine depleting drugs such as reserpine in reducing psychotic symptoms.[13]

Measures of ADRs associated with Antipsychotic drugs

For schizophrenia, antipsychotic drugs are the cornerstone of the pharmacological treatment such as chlorpromazine (first antipsychotic drug) introduced in 1952 that also marked the new era in psychopharmacology.[14] The early antipsychotic drugs are now referred to as first-generation antipsychotics (FGAs) which include chlorpromazine, haloperidol or fluphenazine. As these agents are effective in relieving positive symptoms of the diseases, but they also have serious limitations. They lack the efficacy regarding negative symptoms and the adverse effects especially extrapyrimidal symptoms (EPS) became serious drawbacks of these drugs. The drawbacks of FGAs lead to the development of newer antipsychotics (Respiridone, Olanzepine, Quetiapine etc) which met with great expectations since 1990s. Newer antipsychotics also known as novel antipsychotics are now referred as second generation antipsychotics (SGAs) such as Clozapine.[15]

The first antipsychotic that proved to be affective in the treatment of schizophrenia was clozapine, but also known as the first antipsychotic devoid of extrapyrimidal symptoms (EPS). However clozapine has the ability to cause agranulocytosis as a serious adverse effect

that led to the withdrawal of clozapine by the manufacturer, but reintroduced in 1989 with strict regulations regarding indications and white blood cell count follow-up.[16,17] Antipsychotics are pharmacologically heterogeneous group of compounds that act as D_2 dopamine receptor antagonists, an action linked to their antipsychotic effect.[18] Both typical and atypical antipsychotic drugs may provoke seizures in susceptible patients. The risk of seizures seems highest for clozapine and lowest for Resperidone.[19] The majority of adverse effects of antipsychotics agents are extensions of their pharmacological actions, also there are some allergic and idiosyncratic adverse effects.[20] In general antipsychotic agents have better compliance but also have capability to cause adverse effects. The major adverse drug reactions caused by antipsychotic drugs are pointed out as below.

Sedation and cognition

Chlorpromazine, thioridazine, mesoridazine and the atypical clozapine, olanzepine and quitiapine are the agents are most frequently prescribed agents which may cause sedation.[21] Sedation occurs early in the treatment course and may decrease overtime but oversedation will lead to cognitive perceptual and motor dysfunction.[22]

Extrapyrimidal symptoms (EPS)

Extrapyrimidal symptoms induced by antipsychotic drugs, neurotransmitter imbalance between D2 dopaminergic neurons with a hypoactivity and M4 muscarinic cholinergic neurons with hyperactivity occurs. The neurotransmitter alterations in Parkinson's disease have been described as follows: dopamine and GABA hypoactivity and acetylcholine and glutamate hyperactivity. Dopamine hypoactivity occurs after treatment with FGAs and SGAs. Dopaminergic neurons in the substantia nigra activate D1 and D2 dopaminergic neurons located in the caudate nucleus. In this nucleus, D1 dopaminergic neurons weakly activate dynorphin neurons, which inhibit via mu receptors substance P neurons.[24, 25]

The latter neurons activate GABAergic neurons in the internal globus pallidus. D2 dopaminergic neurons activate GABAergic neurons in the external globus pallidus.[26] When extrapyramidal symptoms occur, a dopaminergic-cholinergic neurotransmitter imbalance appears due to the blockade of the D2 receptor in the extrapyramidal system. In the internal globus pallidus, GABAergic neurons weakly inhibit, via GABAA receptors, M4 muscarinic cholinergic neurons located in the putamen and enhance acetylcholine hyperactivity. Consequently, M4 receptor antagonists can counteract the dopaminergic-cholinergic neurotransmitter imbalance in the extrapyramidal system.[27]

Extrapyrimidal symptoms are serious, sometimes deliberating and stigmatizing adverse effects and require additional pharmacotherapy and include acute dystonias, akathisia, Parkinsonism and Tardive dyskinesia (TD). EPS develop into two phases, early acute EPS most often develop upon the beginning of pharmacotherapy or when the dose of antipsychotic drug is increased. The later onset EPS usually occurs after prolonged manifestations include akathisia, acute dystonia, and Parkinsonism.[28, 29] Acute dystonia occurs mainly within first few days after starting antipsychotic treatment. The primary risk factors for acute dystonia are young age and male gender, history of substance abuse and family history of dystonia. Acute dystonia can be effectively prevented or reversed with anticholinergic drugs such as biperiden.[30-34]

Akathisia occurs mostly within the first three months of treatment and is very common, poorly understandable and difficult to treat. The effective treatment for akathisia is dose reduction, liposoluble beta adrenergic blockers and benzodiazepines.[30, 31] About 25 % of patients treated with first generation antipsychotics develop Akathisia.[30] Second generation antipsychotics such as clozapine and Quetiapine have the lower risk of akathisia, but not confirmed in blinded reviews.[35] Tardive dyskinesia (TD) includes symptoms like involuntary, repetitive movements such as grimacing, tongue protruding, oculogyric crisis and lips puckering as well as torso and limb movements.[36, 37] Tardive dyskinesia (TD) may occur after the discontinuation of pharmacotherapy or even may be irreversible. It is estimated that about 50% patients treated with high potency first generation antipsychotics such as haloperidol develop acute extrapyrimidal symptoms (EPS) within the first several days of treatment. Prevalence of Tardive dyskinesia is less known due to differences in design and methodologies among the studies that have investigated this problem[21, 22, 31] and some studies have reported the prevalence of TD as 0.5% to 70% of patients receiving FGAs, with an average rate being between 24% and 30%.[38, 39] Acute EPS usually responds to dose reduction of the antipsychotic agent or require additional pharmacological treatment. Antipsychotics induced Parkinsonism occurs between few days and upto several months after the treatment is initiated. Risk factors that are related with antipsychotic induced Parkinsonism are age (mainly elderly), gender (female), early onset EPS and cognitive deficit.[40] This type of Parkinsonism is considered reversible as well as anticholinergic agents may be useful, but anticholinergic agents should be avoided in the elderly patients due to their side effects such as cognitive deterioration, urinary retention, dry mouth and risk of glaucoma exacerbation. The rates of Parkinsonism induced by SGAs (e.g., 26% with

olanzepine) are lower than those with FGAs (55% with haloperidol), but are not negligible, so switching to SGAs is often recommended in cases of Parkinsonism.[41]

Hyponatraemia

Hyponatraemia is state of imbalance in water-electrolyte homeostasis generally defined as a lowered serum sodium level of <136mmol/L (normal level is 136-144mmol/L).[42] Hyponatraemia is seen in about 4% of patients who have chronic schizophrenia and also in patients with other psychiatric disorders such as psychotic depression, manic depressive psychosis and mental retardation.[43-45] Severe or rapidly developing hyponatraemia can cause convulsions, coma and even death and also it has been associated with the development of rhabdomyolysis.[46, 47] It was recognized in 1970s that antipsychotics such as tiotixene (a thioxanthene derivative) and haloperidol (a butyrophenone derivative) may impair the ability of patients to excrete a free water load.[48, 49] It was shown that a greater portion of elderly patients treated with phenothiazines such as chlorpromazine, thioridazine and fluphenazine had significantly lower serum sodium levels than patients not treated with phenothaizines.[50] It was also shown that a greater portion of patients treated with haloperidol had impaired free water excretion and urinary dilution than healthy controls.[51] These symptoms have not been reported for newer atypical antipsychotic agents but some case reports of drug-induces hyponatraemia in patients using atypical antipsychotics suggests that atypical antipsychotics also affects water balance and can induce hyponatraemia in some cases.[52, 53]

Sexual dysfunction

Sexual dysfunction (SD), defined as any reduction in desire or libido, diminished arousal, decline in the frequency of intercourse, or an undesirable inability to achieve orgasm.[54] SD is very common in patients taking antipsychotic drugs with prevalence of 45-80% in males and 30-80% in females.[55] A study shows about 49% of patients who take antipsychotic drugs show sexual dysfunction.[56] The mechanism involved in the sexual dysfunction is associated with elevation of prolactin level as suggested by various studies.[57] The mechanism of antipsychotics is mainly dopamine blockade. Blockade of dopamine receptors by antipsychotics in the tuberoinfundibular tract releases the inhibition of prolactin storage cells that result in the elevation of prolactin level.[58] Due to the elevated prolactin levels, it has been shown to have profound effects on reproductive health as well as sexual function including hypogonadism, decreased libido in sexes, amenorrhea and infertility in women and low sperm count and reduces muscle mass in men.[59] In elderly patients increase in prolactin

levels can cause galactorrhea in women and men also gynecomastia in men; mainly these effects are more common with the atypical antipsychotics and with Respiridone and can be dose related.[21]

Weight gain

Weight gain is common and substantially significant side effect of antipsychotic agents in both adults and children such as olanzepine and clozapine than other atypical antipsychotic agents i.e., >7% of the baseline body weight in 40% or more of patients.[21, 60-62] Weight gain is well established adverse effect of acute and maintenance antipsychotics treatment in patients with schizophrenia which affects between 15% and 72% of patients with some evidences suggests that similar effects occur in patients with bipolar disorder.[63-66] Among first generation drugs known as low potency agents such as chlorpromazine and thioridazine are mainly associated with a higher risk of weight gain, but risk is greatest with the use of second generation antipsychotics such as clozapine and olanzepine. Antipsychotics agents such as iloperidone, Quetiapine, Respiridone, paliperidone, sertindole and zotepine have intermediate risk of weight gain.[67] Factors that are responsible for patients risk of antipsychotic drug induced weight gain include demographic variables, treatment settings i.e., inpatient versus outpatient, illness characteristics, past and current treatment with antipsychotics and other medications etc.[68]

Neuroleptic malignant syndrome

A fatal reaction associated with the use of antipsychotic drugs is neuroleptic malignant syndrome (NMS) but is rare. NMS typically evolves during the first week after the initiation of antipsychotics, but can develop at anytime. NMS is characterized by muscle rigidity with myonecrosis, a delirium that resembles catatonia and dysfunction of autonomic nervous system with hyperthermia, tachycardia and hypertension or hypotension. The major complications of NMS include cardiopulmonary arrest, aspiration pneumonis, myoglobinuric renal failure and disseminated intravascular coagulation with special reference to Clozapine.[69, 70] The death rate was found to be 9% and serious adverse effects were reported for 20% of the cases out of 77 cases of neuroleptic malignant syndrome with patients aged 18 years or younger.[71]

Other side effects of Antipsychotics

Constipation is a common side effect of antipsychotics but discusses very little. Antipsychotics differ in their ability to induce constipation, but clozapine is the common

agent responsible for constipation. Constipation can be severe and may lead to serious consequences such as paralytic ileus, bowel occlusion and death.[72] Hypersalivation,[73] fever,[74] nausea, and nocturnal enuresis[75] may also occur. Less reported common side effects are colitis, delirium, eosinophilia, heat stroke, hepatic failure, pancreatitis, pericardial effusion etc.[76]

Prophylaxis and management of ADRs

An early detection of the cause of ADR and proper treatment of anaphylaxis are essentially required for successful management. The most appropriate therapy includes the use of epinephrine, oxygen, vasopressors, corticosteroids and adequate fluid replacement. Acute therapy in emergency is directed towards oxygenation and maintenance of normotension. ADR needs to be differentiated from other symptoms to avoid the discontinuation of the necessary drugs. Adverse drug reactions can be minimized through use of established protocols for premedication or through desensitization achieved with graduated schedules. A complete and thorough knowledge of drugs causing immunological reactions, patient's history of allergy, if any and mastery overuse of satisfactory alternatives against hypersensitivity is must. Rapid action is sometimes important because of the serious nature of a suspected adverse drug reaction, for example anaphylactic shock. Emergency treatment and withdrawal of all medicines is occasionally essential, in which case cautious reintroduction of essential medicines should be considered. Otherwise, using clinical benefit-risk judgment, together with help from investigations, one decides which medicine(s) should be withdrawn as a trial. The patient should be observed during the withdrawal. The waiting period will vary, depending on the rate of elimination of the drug from the body and the type of pathology. If the patient is clearly getting better, in keeping with the prediction, alternative medicines for the basic disease can be introduced if necessary. If the patient is not doing well after withdrawal of the first drug, the next most likely culprit should be considered, and the process repeated.

If a patient cannot manage without a medicine that has caused an adverse reaction, provide symptomatic relief while continuing the essential treatment. However, when treating an adverse drug reaction, it is important not to introduce more medicines than that are essential. Always have a clear therapeutic objective in mind, do not treat for longer than is necessary, and review the patient regularly and look for ways to simplify management.

Change in approach to medication development

Schizophrenia is not a single disease entity and that the positive symptoms of psychosis i.e., delusions, hallucination, etc which antipsychotics work best to treat, are only one aspect of the disorder's pathology. We are improving our knowledge of what different treatments can do and cannot do, we still remain a long way from being able to recommend with precision, specific treatment for individual patients, in terms of clinical response and lack of adverse events. There is also lack of knowledge to identify those patients who will and who will not require long term antipsychotic medications with first generation antipsychotics and second generation antipsychotics. We need to focus on future pharmaceutical developments on symptoms domain of schizophrenia. A more concentrated focus on symptom domains may lead to endophenotypic markers being identified for negative symptoms and cognitive deficits as well as for positive symptoms that can promote novel medication discovery. If medications are discovered for individual and separate symptom domains of schizophrenia, then we could expect to be able to develop concurrent medication strategies, with antipsychotics used in combination with medications for negative symptoms or along with those that have cognitive enhancing effects.

CONCLUSION

ADR or drug toxicity is a common problem that threatens the safety and health status of patients, but as the whole represents burden on the whole healthcare systems. Since clinical diagnosis of adverse drug reactions is not possible hence there is need to implement proper system to identify and manage adverse drug reactions. Adverse drug reactions are often poorly diagnosed and documented in day to day medical practice. Antipsychotics are among the most safe and effective drugs. However, sometimes they cause adverse effects. As we accumulate more and more information on drug responses, we must not lose sight of the sobering fact that about half the cases of drug-related injury are from potentially avoidable adverse drug reactions. Early detection, evaluation and monitoring of ADRs are essential to reduce harm to patients and thus improve public health. Hence there is a need for an active surveillance system to detect and monitor the harmful drugs that have entered into the market. Health care professionals should be aware about the need of reporting and properly documenting ADRs. Polypharmacy should be discouraged as maximum ADRs occur due to drug-drug interaction. Early signals of irrational use of drugs can be detected by frequent auditing. Also Pharmacovigilance needs to be enforced in our health care system to improve better and safe use of drugs.

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