

A Review on ADRs due to Antipsychotic Drugs

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Abstract

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”. A psychosis is a mental disorder characterized by a disconnection from reality. Antipsychotics are the most effective drugs which are used in the psychiatry in the maintenance therapy of mania, psychoses and schizophrenia. The antipsychotics drugs are chemically disparate but have the common property of alleviating the symptoms of organic as well as functional psychosis. But they also have a capacity to cause a wide range of potential adverse drug reactions that can lead to non-compliance that can impair quality of life, may cause the extra pyramidal symptoms which can lead to discontinuation of therapy and in extreme cases it may be fatal. Knowledge of assessment of ADR due to different antipsychotics is necessary. It helps to choose to safe treatment and reduce the risk of occurrence of ADRs by the clinicians. Antipsychotics exhibit their own spectrum of adverse effects including hypotension, seizures, weight gain, increased risk of diabetes mellitus, hyperlipidemia. Occurrence of ADR had largely affected hospital stay of patients indirectly influencing economic burden on patients. ADR are often poorly identified and reported in day to day medical practice. As we collect more and more information about ADRs, we need an active surveillance system regarding identification and reporting of ADRs with antipsychotic drugs.

Keywords: WHO, Adverse Drug Reactions, Pharmacovigilance, Typical and Atypical Antipsychotic Drugs.

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} A psychosis is a mental disorder characterized by a disconnection from reality.{2} Antipsychotics are the most effective drugs which are used in the psychiatry in the maintenance therapy of mania, psychoses and schizophrenia.{3} The antipsychotics drugs are chemically disparate but have the common property of alleviating the symptoms of organic as well as functional psychosis.{4} But they also have a capacity to cause a wide range of potential adverse drug reactions that can lead to non-compliance that can impair quality of life, may cause the extra pyramidal symptoms which can lead to discontinuation of therapy and in extreme cases it may be fatal.{5} Antipsychotics drugs have a broad spectrum of therapeutic effect in clinical practice and are generally safer agents. Adverse effects are augmentation of many pharmacological actions of these drugs such as central, cardiovascular, autonomic nervous system, and endocrine system.{5,6-8} Knowledge of assessment of ADR due to different antipsychotics is necessary. It helps to choose to safe treatment and reduce the risk of occurrence of ADRs by the clinicians.{9} The second generations of antipsychotic drugs are differ from the first generation as they have a low risk of adverse reactions such

as extra pyramidal symptoms and also reduce the positive and negative symptoms of schizophrenia.{10} Besides low tendency of exhibiting a Extra pyramidal symptoms, second generation antipsychotics exhibit their own spectrum of adverse effects including hypotension, seizures, weight gain, increased risk of diabetes mellitus, hyperlipidemia.{10-12} These ADRs are not only common but also have a high rate of preventability. The selection of medicines should be targeted for quality improvement patient healthcare system. It can be done by the data use of frequency, severity, probability and preventability. After getting all the information of high-risk drugs through analysis may have significant impact on reducing the ADRs. {13} Hence, an attempt has been made in this article exhibit an updated analysis of ADRs which are caused by antipsychotics drug and how to manage the ADRs in general outlook and what are the future outcomes in the management of adverse drug reaction.

PHARMACOKINETICS OF ANTIPSYCHOTIC DRUGS

Mostly, all the antipsychotics drugs are readily but incompletely absorbed. Many drugs undergo first pass metabolism. The oral administration of Chlorpromazine & Thioridazine have systemic availability of 25-35%, whereas Haloperidol systemic availability of about 65%.

Antipsychotic drugs are highly lipid soluble & protein bound i.e., 92 to 99%. They also have a large volume of distribution (i.e., >7L/Kg). They have long duration of action than would be estimated from their plasma half-lives. Symptoms of psychoses will be reoccurrence in 6 months after the discontinuation of treatment.

Antipsychotics drugs are metabolized by the oxidation, demethylation, catalysed by liver microsomal CYP-P450 enzymes, CYP2D6, CYP1A2, CYP3A4. The elimination t_{1/2} is variable, but mostly is in the range of 18-30 hrs. The metabolites are excreted in urine & bile weeks after the discontinuing of treatment. The broad spectrum of pharmacokinetics of neuroleptics is similar. {14}

PHARMACODYNAMICS OF ANTIPSYCHOTIC DRUGS

Mechanism of action of all the antipsychotics in the brain is D₂ receptors antagonism that has given rise to the hypothesis that schizophrenia and other positive and negative symptoms. Positive symptoms may occur by the dysregulation of dopaminergic circuits with excess dopaminergic activity in mesolimbic pathway and negative symptoms due to the dopaminergic signaling in the mesocortical pathways. The affirmation for the dopamine hypothesis comes from not only the potency of D₂ receptor antagonism, but also the effect of D₂ agonists such as amphetamine in precipitating psychosis and the effect of dopamine depleting drugs such as reserpine in reducing psychotic symptoms. {15}

For Schizophrenia, antipsychotic drugs are the cornerstone of the pharmacological treatment such as chlorpromazine which is introduced in 1952 as a first-generation antipsychotic drug. {16} The early antipsychotic drugs are also come in the market as Chlorpromazine, Haloperidol, Fluphenazine are referred to as first generation antipsychotics. These drugs are affecting in relieving positive symptoms but also exhibit an extra pyramidal symptoms, tardive dyskinesia. Because of limitation of these agents may lead to introduced of newer antipsychotics drugs in 1990 such as resperidone, olanzepine, quetiapine, etc. Newer antipsychotics are now termed as second-generation antipsychotic drugs which have a low risk of causing an extra pyramidal symptoms, tardive dyskinesia and also have frequency of producing some adverse drug reactions such as weight gain, metabolic changes and associated cardiovascular consequences. {17}

The first-generation antipsychotics are effective in the treatment of Schizophrenia but also have tendency to exhibit extra pyramidal symptoms and lead to tardive dyskinesia. However, clozapine withdrawal from the market by manufacturers because it have ability to produce agranulocytosis but later it is reintroduced in the market with strict regulations as white blood cell count follow up and other investigations. {18,19} All the antipsychotics are effective by binding on D₂/D₃ receptors in the ventral striatum. {20} Both first and second generation antipsychotics is associated with a clear, dose-dependent risk of seizure provocation. The risk of seizure provocation is high with first generation antipsychotic drugs as compared to second generation antipsychotic drugs. The risk of seizure seems higher for clozapine and lowest for Resperidone. {21} The majority of adverse effects of antipsychotic drugs are extensions of their pharmacological action, also these are some adverse effects. {22} In general, antipsychotics drug have better mainstay in the treatment of psychoses and other

mental problems but also have tendency to cause adverse effects.

These are the adverse drug reactions which is associated by antipsychotic drugs are as follows –

Extra pyramidal Symptoms

It can be induced by antipsychotic drugs, neurotransmitter imbalance between hypoactivity of D₂ Dopaminergic neurons and hyperactivity of M₄ Muscarinic cholinergic neurons. Dopamine, GABA hyperactivity cause a parkinsonism disease. Dopamine hyperactivity occurs after treatment with first generations and second generations. {23,24,25} Antipsychotic drugs cause four main extra pyramidal symptoms such as parkinsonism, acute dystonia, akathisia and tardive dyskinesia. {26,27} The first three mainly begin within a few weeks of treatment or dose increased.

Dystonia

It is spastic contractions of muscles. These reactions are uncomfortable and can be life threatening if left untreated. It occurs within hours or days after administration of antipsychotic drugs. {28} The risk factors of dystonia are young age, history of drug abuse and family history of dystonia. {29,30,31} It can be treated with anti-cholinergic drugs or antihistaminic. {32-37}

Akathisia

It is a movement disorder characterized by subjective feelings of internal restlessness or jitteriness that can be manifested as repetitive movements such as leg crossing, swinging or persistent shifting from one feat to another. {38} It occurs mostly within first three months of treatment and is very common, poorly understandable and difficult to treat. {39} About 25% of patients treated with first generation antipsychotic drugs develop akathisia. {32} Second Generation Antipsychotics Drugs such as Clozapine and Quetiapine have the lower risk of akathisia, but not confirmed in blinded reviews. {40} Treatment of akathisia can include dosage reduction or the addition of β -blockers or anti-cholinergic drugs. {32,33,41,42}

Tardive dyskinesia

It is an abnormal involuntary movement disorder that can be caused by long-term antipsychotic treatment. It may not be reversible if the treatment is discontinued. Abnormal movements may include myoclonic jerks, tics, grimacing, tongue protruding, lips puckering as well as torso and limb movements. {43,44} Prevalence of Tardive dyskinesia is less known due to differences in design and methodologies among the studies that have investigated this problem. {33,45,46} Mainly, acute extra pyramidal symptoms usually treat to dose reduction of antipsychotic drugs, or require additional pharmacological treatment. {47-50}

Parkinsonism

Parkinsonism include bradykinesia, rigidity and tremor. It is a reversible syndrome and the risk factors are age (mainly elder patients), gender (female), early onset extra pyramidal symptoms and cognitive deficit. {51,52} Additional risk factors include pre-existing rigidity {53} and AIDS. {54,55} Treatment of parkinsonism include dosage reduction and anti-cholinergic drugs, {56,57} but anti-cholinergic drugs should be avoided in elderly patients due to

their side effects such as urinary retention, dry mouth, risk of glaucoma exacerbation.{58,59}

Sedation

Antipsychotic drugs have a sedative effect, which is related to dosage and affinity for Histamine H1 receptor.{39} Sedation occurs early in the treatment course and may decrease over time, but its effects can be mistaken for the cognitive, perceptual and motor dysfunction.{45,46} Sedation can occur with first generation antipsychotic drugs (such as Chlorpromazine, thioridazine & mesoridazine) and second generation antipsychotic drugs (such as Clozapine, Olanzapine & Quetiapine),{6,47} but it is seen more commonly & tends to be severe with low-potency first generation antipsychotic drugs than with second generation antipsychotic drugs. The management of Sedation occur Shifting dosing to night-time and reducing total daily dose.{60}

Anti-cholinergic effects

Anti-cholinergic effects include constipation, urinary retention, dry mouth, blurred vision.{61} These effects are common with low potency first generation antipsychotics and clozapine.{62,63}

Hyperprolactinemia

It occurs mostly within a few weeks of beginning of treatment or increasing the dosage but can also arise after long-term stable use. It is a common with the use of any first-generation antipsychotic drugs as well as second generation antipsychotic drugs such as Risperidone and is dose dependent.{64} An increase in prolactin levels may cause by blocking of dopamine in hypothalamus and it results, galactorrhoea in men.{65} Hence, physicians routinely measure the serum prolactin levels.

Cardiovascular

All antipsychotic may cause ECG changes such as prolonged QT interval and orthostatic hypotension.{45} Orthostatic hypotension occur with the low-potency first generation antipsychotic drugs such as Chlorpromazine, thioridazine and with second generation antipsychotic drugs such as Clozapine, Risperidone, Olanzapine, Quetiapine.{66} Antipsychotics most likely to cause ECG changes are low potency first generation antipsychotic drug such as thioridazine and the second generation antipsychotic drug such as Ziprasidone.{45,67}

Sexual Dysfunction

Sexual dysfunction refers to as reduction in desire or libido, diminished arousal, decline in the frequency of intercourse.{68} It is very common and up to 49% of patients taking antipsychotic drugs report problems with sexual dysfunction, a distressing adverse effect that can lead to poor medication adherence.{69} Both FGAs and SGAs drugs can impair arousal and orgasm in men and women. Galactorrhea in women and men also gynecomastia in men are more common with second generation antipsychotics and with risperidone and can be dose related.{70}

Weight Gain

The common adverse effect of antipsychotic drugs are weight gain which can be rapidly increase and difficult to control. It doesn't dose-dependent and substantially significant side

effect of antipsychotic drugs and mainly reported in adults and children. Olanzapine and Clozapine may cause more weight gain as compared to other atypical antipsychotic drugs such as >7% of the baseline bodyweight in 40% or more of patients.{45,70-72} It can also induce cardiovascular and cerebrovascular morbidity and mortality reduced quality of life and poor drug compliance. The first-generation antipsychotic drugs such as Chlorpromazine and thioridazine cause high risk of weight gain but risk is greatest with use of second-generation antipsychotic drugs such as Clozapine and Olanzapine. Antipsychotic drugs such as Quetiapine, Risperidone, Paliperidone, Sertindole, Zotepine have intermediate risk of weight gain.{73} These are the factors which are responsible for the risk of weight gain due to antipsychotic drugs at re-demographic variables, treatment settings, illness characteristics, history and current treatment with antipsychotics and other drugs etc.{74}

Neuroleptic Malignant Syndrome

A life-threatening reaction may cause by the use of antipsychotic drugs but it is rare. It can be initiated within first week of treatment of antipsychotics but can develop at any time. NMS is characterized by labile blood pressure, tachypnoea, tachycardia, sialorrhoea, and flushing, skin pallor. The idiosyncratic reactions to antipsychotic drugs include cardiopulmonary arrest, aspiration pneumonias, myoglobinuric renal failure with special reference to Clozapine.{75,76} Up to 9% of total death rate was reported and out of 177 cases 20% of cases of NMS with patients aged 18 years or younger were reported as serious adverse drug reactions.{77}

Other Side effects of Antipsychotic Drugs

Some of the ADRs are very common but discussion and reporting are very little such as constipation, fever, hypersalivation, nausea, colitis, delirium, eosinophilia, heat stroke, hepatic failure, pancreatitis, nocturnal enuresis. Clozapine is the most common agent which is responsible for the constipation. It can be severe and may lead to serious problems such as ileus, bowel occlusion and sometimes may be death.{78-81}

IMPLICATIONS AND MANAGEMENT

The burden of ADRs with the use of psychiatric drugs varies among studies. The range of implicated agents is diverse but antidepressant and antipsychotic drugs are most commonly associated with ADRs. These are the key points which is helpful in management of ADRs and facilitating the well being of patients –

- i) Clinicians have to be aware about all the ADRs which are associated from antipsychotic drugs.
- ii) The need to balance the potential risks with expected benefits has to be kept in mind by clinicians,
- iii) Treatment is individualized as per patient basis such as diagnosis, age, physical status, other factors like co-morbid conditions, other history of medications, patient past response, nutritional status and so on.
- iv) Clinicians should be keep in mind that medication prescriptions should be accompanied by appropriate device.

- v) When a patient on antipsychotic drugs, frequent assessment of metabolic parameters, ECG have to done.
- vi) Finally, keep in mind a current literature of patients will help a clinician better formulate a treatment plan, anticipate potential problem, and avoid them.

General procedures for manage ADRs-

- i) Lower the dose – When a antipsychotic drug provided benefit to the patients the ADR is also occur but it is dose-dependent. So, the lowest dose is prescribed to the patients for achieving treatment goals.
- ii) Switch to an antipsychotic drug – It can be relevant when the dosage adjustment cannot be proven beneficial for the patients and addressed a life- threatening or fatal.
- iii) Prescribed a non- pharmacologic intervention – It proven effective when weight gain and related lipid abnormality was addressed so, the diet and exercise programs are effective.
- iv) Treat with a concomitant medication – These are used for reducing the ADRs which is associated by antipsychotic drugs but they also have own adverse effects. Hence, few concomitant medication approaches are supported by evidence from randomized controlled trials.

CONCLUSION

Occurrence of ADR had largely affected hospital stay of patients indirectly influencing economic burden on patients. ADR are often poorly identified and reported in day to day medical practice. As we collect more and more information about ADRs, we need an active surveillance system regarding identification and reporting of ADRs with antipsychotic drugs.

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