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A CLINICALLY SIGNIFICANT DRUG – DRUG INTERACTIONS IN PSYCHIATRY

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Abstract:

Patients with psychiatry are often exposed drug-drug interactions, the main aim of the study isto investigate the drug interactions in the psychiatric patients. Most clinically significant druginteractions are pharmacodynamic (PD) and pharmacokinetic (PK) that results in augmented or antagonistic actions at a receptor. In metabolism, the major enzymes which are involved in drug interactions of psychotropic drugs are Cytochrome P450 (CYP) System. Drug-druginteractions are said to play a Significant and important role in the occurrence of adverse drugreactions. The major drug interactions in psychiatry are caused by haloperidol, clozapine, olanzapine, amitriptyline, amisulpride etc.. Concurrent use of these drugs can increase in QT prolongation and increase in the risk of Ventricular anthymias. The main aim of this study is to describe the drug interactions that causes major effects in psychiatric patients.

***KEY WORDS**: Olanzapine, haloperidol, amitryptaline, sertralin*

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INTRODUCTION:

Combination therapy used in psychiatric practice makes drug interactions more likely & increases the risk of adverse outcomes to patients. In a drug-drug interaction (DDI), the presence of Second drug alters the nature, magnitude, or duration given dose of a first drug. According to recently published study, Medications can a recently published study, psychiatric medications can account for upto to 50% of the ADRs for hospitalized patients with mental illness.[1]Clinicians within the primary care setting are increasingly providing pharmacotherapy management of patients with psychiatric illnesses, with over 25% of primary care patients seeking care for major depression and 14% for schizophrenia. Factors Include the potency & concentration drugs involved, the therapeutic index balanced between efficacy and toxicity, presence of active metabolites,& the extent of the metabolism the Substrate drug.[2]More than 100,000 possible detrimental drug-drug interactions (DDIs) have been documented in the medical literature and pharmaceutical company data.

Fig.1: Drug interactions

Objectives:

The primary objective is to determine the clinically significant drug – drug interactions in psychiatric patients with different antipsychotic drugs.

Pharmacokinetic drug interactions:

Absorption:

Psychiatric drug interactions resulting from impaired absorption are similar to those seen with medical medications. For example, psychiatric patients on certain medication regimens, such as the atypical antipsychotic clozapine, can develop significant constipation, which often requires additional medication to resolve.[3,4] Bulk laxatives such as psyllium, magnesium-based antacids, and lactulose products may reduce the absorption of other drugs if administered at the same time..Itis thought that some interactions, mainly seen with the antiepileptic drugs (AEDs), previously assumed to be a result of CYP450 alterations, instead may actually be mediated by the modulation of the Pgp activity at the point of drug absorption or distribution. In general, chelation is not as much an issue for antipsychotics; however, antacids containing divalent cations (such as calcium and/or magnesium) and sucralfate may impair the absorption of phenytoin.

Metabolism:

Carbamazepine, phenytoin, quetiapine, primelone and phenobarbital.

- Medications that metabolically induced by the isoenzyme CYP1A2, such as clozapine.
- Primarily hepatic metabolism via CYP3A4 to active N-desalkyl quetipine and 2 in active metabolites.

Inhibitory effects of newer antidepressants on CYP450 isoenzymes:

Drug	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Citalopram	0	0	0	1	0
Fluxetine	1	2	1 or 2	3	1 or 2
Fluvoxamine	3	2	3	1	2
Mirtazepine	0	0	0	1	0
Paroxetine	1	1	1	3	1
Serotraline	1	1	1	1 or 2	1
Venlafaxine	0	0	0	1	1

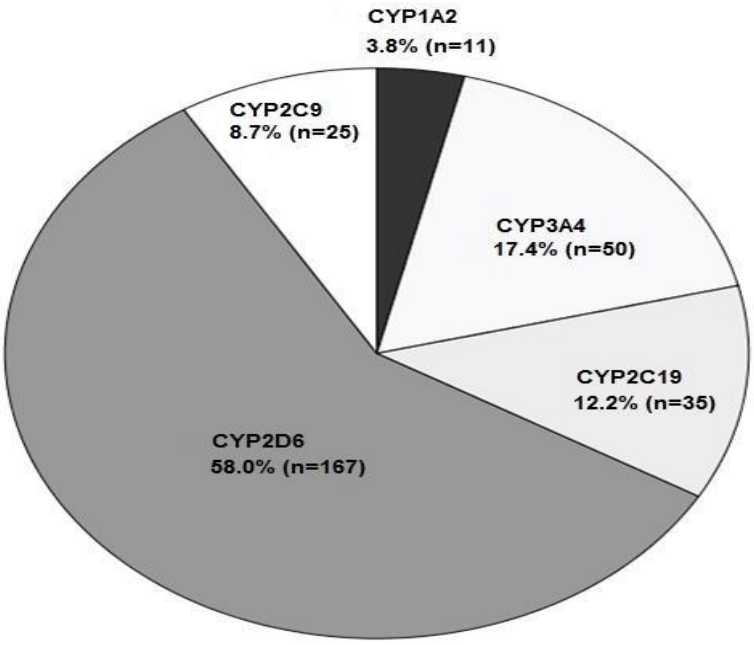

Fig.2: Inhibitory effects of newer antidepressants affecting pharmacokinetic interactions

Distribution:
The risk for protein-binding interactions occurs as the unbound free fraction of the competing drugincreases & becomes more available for metabolism.This is more common for the mood stabilizing AGD, including phenytoin, Valproic acid, diazepam, tiagabine as well as antipsychotics including Clozapine, risperidone, olanzapine & Ziporasidone.[5]

Elimination:
Psychiatric drug interactions that result in altered elimination are rare.An increase in lithium levels can develop over 5 to days after adding on NSAID, & levels can return to baseline serum conc^{n} within 7 days of stopping the NSAID.In the case Suggested ACE inhibitors & ARBs, It has been sudept ggested that there agents the lithium clearance.

Pharmacodynamic drug interactions:
It occurs when drugs acts at the same or interrealated receptor sites, resulting in additive, synergistic, or antagonistic effects of each drug at target receptor.Mostly pharmacodynamic interactions are fairly straight forward & predictable if the practitioner has a basic understanding of drug mechanism of action & receptor effects.

some examples are as follows;

Anticholinergic intoxication:
Synergistic anticholinergic effect of drugs such as tricyclic antidepressants adminstration concurrently with anti-parkinsonism agent can increase anticholinergic effect of anti-psychotics such as clozapine, olanapine & quetipine leading to dry mouth, blurred vision & possibly delirium. Amitriptaline taken concurrently with benztrapine can produce pronounced constipation, heat stroke, urinary retention.[7]

Serotonin syndrome:
Drug categories that should be considered in this possible interaction, include antidepressants, opioids, CNS stimulants,5-HT, anti-depressants, (triptants), dextromethorphan &certain herbal products available. QTC interval such as chlorpromazine and haloperidol, placing the patient at a greater risk of arrythmias.[8]

Blood dyschromia's:
Almost all classes of psychotropic agents have been reported to cause blood dyscarasias such as leukopenia, neutropenia, thrombocytopenia, eosinophilia, anemia, agranulocytosis & altered platelets function. Clozapine is well known as a drug that causes dyscarasis; however many other agents, including olanzapine, antidepressants, mood-stabilizing AEDs &other atypical antipsychotics can also cause blood dyscarasias it mostly affect blood components, lymph tissue orblood vessel they can be cancerous or benign, common or not and they can range from mild to life-threatening.[9]

Other issues:
Co-administration of many anti pychotic agents with conventional agents such as haloperidol or with atypical agents, increase risk of adverse effects such as neuroleptic malignant syndrome result in common adverse effects such as drowsiness,dizziness,orthostatic,hypotension,etc..

Knowledge of CYP enzymes will simplify understanding of pharmacokinetic interactions

- Firstly Drug A effects $\xrightarrow{*}$ CYP enzyme X
- CYP enzyme X metabolizes $\longrightarrow$ B,C,D,E
- Therefore,drug A effects$^{*}\longrightarrow$ B,C,D,E

TYPES OF DRUG INTERACTIONS

- Drug -Drug interactions
- Drug – gene treatment
- Drug –Food interactions
- Drug - allergy interactions
- Drug – Disease interactions
- Drug –Laboratory interactions

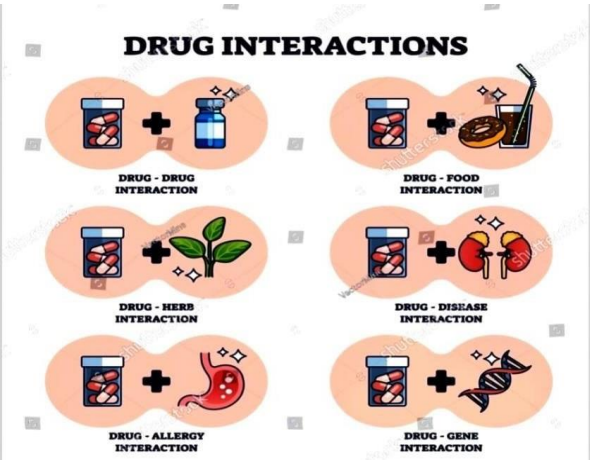

Fig.3: Types of drug interactions

DISCUSSION:

THE POSSIBLE DRUG–DRUG INTERACTIONS IN PSYCHIATRICPATIENT

S.NO	DRUGS	TYPE OF REACTION	INTERACTION
1.	Amitryptaline+Haloperidol	Major	Increased risk of cardiotoxicity
2.	Quetiapine+sertraline	Major	Increased QT interval prolongation
3.	Clozapine+haloperidol	Major	Increased QT interval prolongation
4.	Diazepam+olanzapine	Major	Excess sedation, cardiovascular depression
5.	Alprazolam+diazepam	Moderate	Increased risk of CNS depression
6.	Escitalopram+lithium	Major	Increased risk of sertonin syndrome
7.	Amisulpride + risperidone	Major	Increased risk of ventricular arrthymias
8.	Alprazolam+carbamazepine	Moderate	Decreased alprazolam plasma levels
9.	Amitryptaline+fluoxetine	Major	Increased risk of sertonin syndrome
10.	Olanzapine +sodium valproate	Moderate	Decreased olanzapine plasma level concentration
11.	Haloperidol+lithum carbonate	Major	Increased epilepsy, weakness, brain damage, encephalopathy
12.	Phenytoin + sertraline	Major	Increased risk of phenytoin toxicity and decreased efficacy of sertraline
13.	Sertraline + Tramadol	Major	Increased tramadol exposure & decreased concentrations of active metabolites
14.	Fluvoxamine + olanzapine	Major	Increased risk of olanzapine adverseeffects and exposure
15.	Fluoxetin + Imipramine	Major	Increased risk of tricyclic anti-depressants toxicity
16.	Lorazepam + sodium valproate	Moderate	Increased risk of lorazepam concentration
17.	Carbamazepine + olanzapine	Moderate	Decreased olanzapine exposure & decreased efficacy
18.	Promethazine + quetiapine	Major	Increased risk of QT interval prolongation
19.	Lithium + setraline	Major	Increased risk of sertonin syndrome
20.	Alprazolam + olanzapine	moderate	Increased risk of CNS depression

RESULTS:

1.Amitryptaline + Haloperidol (major)

- Concurrent use of this combination results in increased risk of cardio toxicity

Amitriptyline alomg with haloperidol can cause dose-related prolongation of the QT interval. Theoretically, coadministration with amitriptyline can prolong the QT interval may result in elevated risk of ventricular arrhythmias, including ventricular tachycardia and torsade de pointes, because of additive arrhythmogenic potential related to their effects on cardiac conduction. Haloperidol treatment alone has been associated with a number of reported cases of torsade de pointes and sudden death.[10,11]The majority of cases involved intravenous administration or use of higher than recommended dosages. In general, the risk of an individual agent or a combination of agents causing ventricular arrhythmia in association with QT prolongation is largely unpredictable but may be increased by certain underlying risk factors such as congenital long QT syndrome, cardiac disease, and electrolyte disturbances (e.g., hypokalemia, hypomagnesemia).[12]

Monitor closely:
Haloperidol may increase the serum concentrations of tricyclic antidepressants by inhibiting their metabolism via CYP450 2D6.There have been case reports of seizures associated with this interaction.

Management:
Caution is advised if haloperidol is used in combination with amitriptyline's that prolong the QT interval, particularly when administered intravenously or at higher than recommended dosages. Patients should be advised to notify their physician if they experience excessive tricyclic antidepressant adverse effects such as dry mouth, visual disturbances, urinary retention, dizziness, orthostasis, constipation, and seizures[13].

Chief complaints:

- Involuntary noding of head.
- Generalised body pains
- Decreased food intake
- Decreased sleep and headache

2.Quetiapine + sertraline (major)

- Concurrent use of these medications can increase QT interval prolongation.

Monitor closely:
There is some concern that quetiapine may have additive cardiovascular effects in combination with other drugs that are known to prolong the QT interval of the electrocardiogram. certain agents with anticholinergic properties) may have additive parasympatholytic and central nervous system-depressant effects when used in combination with quetiapine. Excessive parasympatholytic effects may include paralytic ileus, hyperthermia, mydriasis, blurred vision, tachycardia, urinary retention, psychosis, and seizures.[14]

Management:
Coadministration of quetiapine with other drugs that can prolong the QT interval should generally be avoided. Caution and clinical monitoring are recommended if concomitant use is required.[15] In addition, if combination therapy with agents with anticholinergic properties is required, caution is advised, particularly in the elderly and those with underlying organic brain disease. A reduction in anticholinergic dosages may be necessary if excessive adverse effects develop.[16]

Adverse drug reactions:
Quetiapine induced constipation, low blood pressure and cardiac or respiratory arrest.

3.Clozapine + haloperidol (major)

- Concurrent use of this drigs may result in increased risk of QT interval prolongation

Monitor closely:
Coadministration with other psychotropic agents may potentiate the adverse effects of clozapine on cardiovascular function. Orthostatic hypotension with or without syncope, in rare cases accompanied by profound collapse and cardiorespiratory arrest, has occurred during initiation of clozapine treatment alone and in combination with other psychotropic agents, occasionally even on the first dose.[17]

Central symptoms:

It may include memory loss, disorientation, incoherence, hallucinations, psychosis, delirium, hyperactivity, twitching or jerking movements, stereotypy, and seizures.

Management:
The potential for additive effects on the QT interval and increased risk of torsade de pointes arrhythmia should also be considered when clozapine is used in combination with phenothiazines, tricyclic antidepressants, some atypical antipsychotics (e.g., asenapine, quetiapine, iloperidone, iloperidone, paliperidone, risperidone, ziprasidone), or other psychotherapeutic agents that can prolong the QT

interval such as amoxapine, haloperidol, maprotiline, and trazodone.[18,19]Serum electrolytes, including potassium, magnesium and calcium, should be measured at baseline and periodically during treatment, and any abnormalities corrected prior to initiating clozapine. Routine ECG assessment may detect QTcprolongation but is not always effective in preventing arrhythmias.

4.Diazepam + Olanzapine (major)

- Concurrent use of these drugs may result in excess sedation and cardiovascular depression.

Generally, avoid:
The safety and efficacy of intramuscular olanzapine administered in combination with benzodiazepines have not been established.Deaths have been reported in patients who received IM olanzapine during postmarketing use.[20]

Monitor closely:
CNS- and/or cardiorespiratory-depressant effects may be increased during concomitant use of olanzapine and benzodiazepines, especially in elderly or debilitated patients. Risk factors for the increased mortality with olanzapine include age greater than 80 years, dysphagia, sedation, malnutrition and dehydration, concomitant use of benzodiazepines, and presence of pulmonary conditions such as pneumonia.[21]

Management:

Ambulatory patients should be made aware of the possibility of additive CNS effects and counseled to avoid activities requiring mental alertness until they know how these agents affectthem.[22]

Adverse drug reactions:
Sertraline induced giddiness, back pain and insomnia.

5.Alprazolam +Diazepam (moderate)

- Concurrent use of this drugs can cause increased risk of CNS depression.

Monitor closely:
Central nervous system- and/or respiratory-depressant effects may be additively orsynergistically increased in patients taking multiple drugs that cause these effects, especially in elderly or debilitated patients. Sedation and impairment of attention, judgment, thinking, and psychomotor skills may increase.[23]

Management:
During concomitant use of these drugs, patients should be monitored for potentially excessive or prolonged CNS and respiratory depression. Cautious dosage titration may be required, particularly at treatment initiation. Ambulatory patients should be counseled to avoid hazardous activities requiring mental alertness and motor coordination until they know how these agentsaffect them, and to notify their physician if they experience excessive or prolonged CNS effectsthat interfere with their normal activities.

Adverse drug reactions:
Quetiapine induced weight gain,somnolence,itching,body pains.

6.Escitalopram + lithium (major)

- Concurrent use of these drugs increases the risk of sertonin syndrome.

Monitor closely:

Escitalopram can cause dose-dependent prolongation of the QT interval.Theoretically, coadministration with other agents that can prolong the QT interval may result in additive effects and increased risk of ventricular arrthymias.[24,25]The extent of drug-induced QT prolongation is dependent on the particular drug(s) involved and dosage(s) of the drug(s). In addition, central nervous system- and/or respiratory-depressant effects may be additively or synergistically increased in patients taking escitalopram with certain other drugs that cause these effects, especially in elderly or debilitated patients.

Management:
Caution is recommended if escitalopram is used in combination with other drugs that can prolong the QT interval. Symptoms such as dizziness, lightheadedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope.[26]

Adverse drug reactions:
THP induced itching all over the body, sertraline induced diarrhea.

7. Amisulpride + risperidone (major)

- Concurrent use of these drugs can cause increased ventricular arrythmias.

Monitor closely:
Amisulpride can cause dose- and concentration-dependent prolongation of the QT interval. Theoretically, coadministration of other agents that can prolong the QT interval may result in additive effects and increased risk of ventricular arrhythmias including torsade de pointes and sudden death.[27]

Management:
Caution and close clinical monitoring (e.g., electrocardiogram, serum electrolytes) are recommended if amisulpride is used in combination with other drugs that can prolong the QT interval.Adverse drug reactions: dizziness,

lightheadedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope.[28]

8.Alprazolam + carbamazepine (moderate)

- Concurrent use of these drugs can cause decreased alprazolam plasma levels

Monitor closely:

Some antiepileptic agents such as carbamazepine and phenytoin significantly reduce the effect of oral midazolam. The mechanism may be due to enhanced gut and liver metabolism of midazolam (via CYP450 3A4 enzyme induction by carbamazepine). Parenteral midazolam is not likely to be affected. Other oral benzodiazepines metabolized by the 3A4 isoenzyme may interact similarly.[29]

Management:

Patients receiving this combination should be monitored for clinical response. Alternative oral sedative hypnotics may be preferable in patients receiving carbamazepine.

9. Amitriptyline +fluoxetine (major)

- Concurrent use of this medication can cause increased sertonin syndrome.

Generally, avoid:

Pharmacodynamically, the combination of fluoxetine (or any other selective serotonin reuptake inhibitor) and a TCA may potentiate the risk of serotonin syndrome, which is a rare but seriousand potentially fatal condition thought to result from hyperstimulation of brainstem 5HT1A receptors.

Management:

In general, the use of fluoxetine (or other SSRIs) with TCAs should be avoided if possible, or otherwise approached with caution if potential benefit is deemed to outweigh the risk. Pharmacologic response and plasma TCA levels should be monitored more closely whenever fluoxetine is added to or withdrawn from therapy in patients stabilized on their existing antidepressant regimen, and the TCA dosage adjusted as necessary.[30]

Adverse drug reactions:

Amitryptaline induced blurred vision,excess sertonergic activity

10.olanzapine + sodium valproate (moderate)

- Concurrent use of these medications can cause decreased olanzapine plasma levels concentration.

Monitor closely:

Concurrent use of olanzapine and valproic acid may potentiate the risk of hepatotoxicity.In a retrospective study of 52 children, combined treatment with olanzapine and divalproex was associated with more frequent elevations of hepatic enzymes than either agent alone, and meanand peak hepatic enzyme levels during the observed course of treatment were also higher.[31]

Management:

The authors of the study recommend monitoring liver function tests every 3 to 4 months duringthe first year of treatment with either olanzapine or valproic acid, at least in pediatric patients.

Signs and symptoms:

It includes hepatotoxicity such as fever, rash, anorexia, nausea, vomiting, fatigue, right upper quadrant pain, dark urine, and jaundice.

11.Haloperidol + lithium carbonate(major)

- Concurrent use of this medications can cause weakness, increased epilepsy, encephalopathy, and brain damage.

Monitor closely:

Theoretically, coadministration with these agents can prolong the QT interval may result in elevated risk of ventricular arrhythmias, including ventricular tachycardia and torsade de pointes, because of additive arrhythmogenic potential related to their effects on cardiac conduction.Although haloperidol and lithium have been used safely together in many patients, there have been a few reported cases of encephalopathic syndrome consisting of severe neurotoxic effects and extrapyramidal symptoms, followed by irreversible brain damage, associated with the combination.[32]

Management:

Haloperidol is used in combination with lithium, particularly when administered intravenously (not approved by the FDA) or at higher than recommended dosages.Large doses of both drugs should generally be avoided. Some clinicians have recommended reducing the haloperidol dosage when lithium is initiated.

Adverse drug reactions:

Weakness, fever, lethargy, tremulousness, confusion, extrapyramidal symptoms, leukocytosis, and elevations in serum enzymes loss of appetite,right uppeer abdominal pain and sometimes dark urine and yellowish skin.[33]

12.Phenytoin + sertraline(major)

- Concurrent use of this medications may result in increased risk of phenytoin toxicity anddecreased

efficacy of sertraline.

Monitor closely:
The mechanism is thought to be related to inhibition of CYP450 2C9-mediated metabolism of phenytoin by sertraline. Other hydantoins may also be affected. In addition, coadministration of sertraline with potent inducers of CYP450 3A4, such as phenytoin, may result in a reduction in the plasma concentrations and therapeutic effects of sertraline[34].

Management:
Clinical and laboratory monitoring for increased hydantoin levels and toxicity is recommended whenever sertraline is added or dosage is changed.In addition, the potential for diminished therapeutic effects of sertraline should be considered when prescribed in combination with phenytoin.Patients should be closely monitored, and the dosage of sertraline adjusted as necessary.

Adverse drug reactions:
phenytoin induced gingival hyperplasia (gum bleeding)

13.Sertraline + Tramadol (major)

- Concurrent use of these medications may result in increased tramadol exposure and decreased concentrations of active metabolites.

Generally, avoid:
Due to its serotonergic activity, coadministration of tramadol with selective serotonin reuptakeinhibitors (SSRIs) may potentiate the risk of serotonin syndrome, which is a rare but serious and potentially fatal condition thought to result from hyperstimulation of brainstem 5-HT1A and 2A receptors. Pharmacokinetically, coadministration with certain SSRIs, namely fluoxetine, paroxetine and possibly sertraline, may decrease the plasma concentrations of the active O-demethylated (M1) metabolite of tramadol due to inhibition of CYP450 2D6, the isoenzyme responsible for the formation of the metabolite.[35]

Management:
In general, the use of tramadol in combination with SSRIs should be avoided if possible, or otherwise approached with caution if potential benefit is deemed to outweigh the risk.The potential risk for serotonin syndrome should be considered even when administering serotonergic agents sequentially, as some agents may demonstrate a prolonged elimination half-life (e.g., fluoxetine, vortioxetine).[36]

14.Fluvoxamine + olanzapine (major)

- Concurrent use of these drugs may result in increased risk of olanzapine adverse effectsand exposure.

Monitor closely:
Coadministration with potent inhibitors of CYP450 1A2 may significantly increase the plasma concentrations of olanzapine.The greater degree of interaction in smokers is likely due to induction of CYP450 1A2 by polycyclic aromatic hydrocarbons in cigarette smoke, resulting in increased expression of the isoenzyme.

Management:

Pharmacologic response and olanzapine plasma levels should be monitored more closely whenever potent CYP450 1A2 inhibitors are added to or withdrawn from therapy in patients stabilized on their antipsychotic regimen, and the dosage adjusted as necessary.A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or other potentCYP450 1A2 inhibitors.[37]

15.Fluoxetine + Imipramine (major)

- Concurrent use of these medications may result in increased risk of tricyclic antidepressantstoxicity.

Generally, avoid:
Coadministration with fluoxetine may significantly increase the plasma concentrations of sometricyclic antidepressants (TCAs). Pharmacodynamically, the combination of fluoxetine (or any other selective serotonin reuptake inhibitor) and a TCA may potentiate the risk of serotonin syndrome, which is a rare but serious and potentially fatal condition thought to result from hyperstimulation of brainstem 5HT1A receptors.[38]

Management:
Pharmacologic response and plasma TCA levels should be monitored more closely whenever fluoxetine is added to or withdrawn from therapy in patients stabilized on their existing antidepressant regimen, and the TCA dosage adjusted as necessary. For this reason, some authorities recommend a washout period of two to five weeks before and after treatment with fluoxetine.[39]

16.Lorazepam + sodium valproate(moderate)

- Concurrent use of this medications may result in increased risk of lorazepam concentration.

Generally, avoid:
One case series has suggested that benzodiazepines may amplify the teratogenic effects of valproate in the offspring of epileptic women. Both drugs individually have been associated with adverse effects to the fetus.

Management:
Both valproate and benzodiazepines should be avoided during pregnancy unless the potential benefits outweigh the risks to the fetus. In other patients, close observation for clinical evidence of benzodiazepine toxicity is recommended if valproate and a benzodiazepine must be used together.[40]

17.Carbamazepine+ olanzapine(moderate)

- Concurrent use of this medications may result in decreased risk of olanzapine exposure and decreased efficacy.

Monitor closely:
Coadministration with inducers of CYP450 1A2 may decrease the plasma concentrations of olanzapine. Higher daily dosages of carbamazepine may cause an even greater increase in olanzapine clearance. When co-administered with rifampin, a moderate CYP450 1A2 inducer that also induces UGT 1A4, olanzapine peak plasma concentration (Cmax) and systemic exposure (AUC) decreased by 11% and 48%, respectively.

Management:
The potential for diminished pharmacologic effects of olanzapine should be considered during coadministration with CYP450 1A2 inducers. Alternative treatments may be required if an interaction is suspected.[41]

18.Promethazine + quetiapine (moderate)

- Concurrent use of this drugs may result in increased risk of QT interval prolongation.

Generally, avoid:
There is some concern that quetiapine may have additive cardiovascular effects in combination with other drugs that are known to prolong the QT interval of the electrocardiogram. In general, the risk of an individual agent or a combination of agents causing ventricular arrhythmia in association with QT prolongation is largely unpredictable but may be increased by certain underlying risk factors such as congenital long QT syndrome, cardiac disease, and electrolyte disturbances .Excessive parasympatholytic effects may include paralytic ileus, hyperthermia, mydriasis, blurred vision, tachycardia, urinary retention, psychosis, and seizures.[42]

Management:
Coadministration of quetiapine with other drugs that can prolong the QT interval should generally be avoided. Caution and clinical monitoring are recommended if concomitant use is required. the occurrence of torsade de pointes such as dizziness, lightheadedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope. Ambulatory patients should be counseled to avoid activities requiring mental alertness until they know how these agents affect them.A reduction in anticholinergic dosages may be necessary if excessive adverse effects develop.

19. Lithium + Sertraline (major):

- Concurrent use of this drugs may result in increased risk of serotonin syndrome.

Monitor closely:
Lithium may enhance the pharmacologic effects of selective serotonin reuptake inhibitors (SSRIs) and potentiate the risk of serotonin syndrome, which is a rare but serious andpotentially fatal condition thought to result from hyperstimulation of brainstem 5-HT1A and 2A receptors. The exact mechanism by which lithium increases serotonergic activity is unknown.[44] The interaction has been reported with fluoxetine and fluvoxamine and the serotonin-norepinephrine reuptake inhibitor venlafaxine. Symptoms of the serotonin syndrome may include mental status changes such as irritability, altered consciousness, confusion, hallucinations, and coma; autonomic dysfunction such as tachycardia, hyperthermia, diaphoresis, shivering, blood pressure lability, and mydriasis; neuromuscular abnormalities such as hyperreflexia, myoclonus, tremor, rigidity, and ataxia; and gastrointestinal symptoms such as abdominal cramping, nausea, vomiting, and diarrhea.[43]

Management:
Caution is advised if lithium is prescribed in combination with SSRIs. Lithium levels should be assessed regularly and the dosage adjusted accordingly. Patients should be closely monitored for symptoms of the serotonin syndrome during treatment. Particular caution is advised when increasing the dosages of these agents. Moderately ill patients may also benefit from the administration of a serotonin antagonist (e.g., cyproheptadine, chlorpromazine). Severe cases should be managed under consultation with a toxicologist.

20.Alprazolam + Olanzapine (moderate):

- Concurrent use of this medications may result in increased risk of CNS depression.

Generally, avoid:
The safety and efficacy of intramuscular olanzapine administered in combination with benzodiazepines have not been established Based on estimated

exposure, the incidence of fatal reports was less than 0.01%, which is similar to that reported for other parenteral agents used to treat patients with acute agitation associated with mental illness. Deaths have been reported in patients who received IM olanzapine during post marketing use[45].

Monitor closely:
Risk factors for the increased mortality with olanzapine include age greater than 80 years, dysphagia, sedation, malnutrition and dehydration, concomitant use of benzodiazepines, and presence of pulmonary conditions such as pneumonia. Limited data in 15 healthy subjects receiving IM olanzapine followed by an IM benzodiazepine (lorazepam) found that the combination prolonged somnolence by 3.3 hours compared to IM olanzapine alone and 5.8 hours compared to IM lorazepam alone.

Management:
Concomitant administration of IM olanzapine and parenteral benzodiazepine has not been studied and is therefore not recommended. Patients given this combination when necessary, should be closely monitored for excessive sedation and cardiorespiratory depression.[45]

Adverse drug reactions:
Allergic reactions, blemishes on the skin, diarrhea memory impairment neuroleptic malignant syndrome etc..

Other factors in drug interactions:

- Genetics
- Age
- Weight
- Sex
- Lifestyle (diet and exercise).

1. Genetics:
Variations in individual genetic makeup can make the same drug work differently in different bodies.In general,some people because of their genetic code they process certain medications more quickly or more slowly than others.This may also cause the drug levels to go down or goup more than expected.

2. Age:
The kidneys,liver and circulatory system may slow down upon age.As this may causes the drug interaction for various drugs.This can slow down the breakdown and removal of drugs from ourbodies.

3. Weight:
Weight changes could affect dosage and also increase or decrease the risk of drug interactions. So if you have a substantial change in your weight, you may need a different dosage of some medications. Some drugs are dosed according to how much a person weighs.For example doctors prescribed trusted source varying strengths of low weight heparin, such as enoxaparin, and antibiotics, such as vancomycin, depending on a person's body weight.

4. Sex:
Differences between the sexes, such as anatomy and hormones, can play a part in drug interactions. For example, studies show that men metabolize zolpidem (Ambien) at double therate of women.

5. Lifestyle (diet and exercise):
Certain diets can be problematic when combined with medication. For example, research has shown that high fat intake can reduce the response of bronchodilators, which people with asthma use to treat symptoms. Exercise can also change how medications work.

For example, people who take insulin to treat diabetes can experience hypoglycemia (low blood sugar) during exercise. So they may need to adjust the time they eat and take their insulin to offsetthe drop in blood sugar. Smoking cigarettes can also affect the metabolism of some drugs. Be sure to tell your doctor that you smoke if they're recommending you start a new medication. High levels of vitamin K in the diet can also inhibit the blood thinning medication warfarin. Thisinteraction is when the use of a drug alters or worsens a condition or disease. Additionally, some medical conditions can increase the risk of side effects from specific drugs. Some medications can interfere with specific laboratory tests. This can result in inaccurate test results.

CONCLUSION:

Drug interactions in psychiatric patients include potency and concentration of the drugs. various drug drug interactions by using case examples have been discussed. Pharmacokinetic interactions contain absorption, distribution, metabolism, and elimination. whereas pharmacodynamic interactions include anticholinergic intoxication, sertonin syndrome, blood dyscarias and many other issues. Drug drug interaction alters the nature, magnitude or duration and dose of the first drug. Clinically significant drug interactions in psychiatry can have serious consequences on treatment outcomes and patient safety. Awareness, understanding, and proactive management of drug interactions are vital for optimizing psychiatric treatment. It also includes various other factors which may lead to drug interactions such as age, diet lifestyle, sex, weight, genetics exercise..etc.these may also alter the drug-drug interactions in pschiatry. however, there are majordrug interactions which has been discussed and

also includes moderate and minor interactions which cause severe effects.

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