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A Review Article On Clinically Significant Drug - Drug Interaction In Psychiatry

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Abstract: Drug therapy may become even more complex due to the influence of genetic variability on the pharmacodynamics and/or pharmacokinetics of the psychiatric drug. DDIs that are pharmacokinetically mediated include those that are mediated by transport proteins and cytochrome P450 (CYP) enzymes. Every one of these regulatory proteins' functions in drug pharmacokinetics is examined, along with how genetically determined variations in their functional activity might change how a drug accumulates in the body. Psychotropic medication prescriptions have increased in recent years due to the growing number of individuals seeking treatment for various psychiatric diseases in primary care settings. The increasing use of psychotropic drugs is accompanied by notable disparities in the prescribing practices of primary care physicians and psychiatrists. Prescription procedures that involve the simultaneous administration of many psychiatric medications have increased the likelihood of drug-drug interactions. Adverse drug responses (ADRs) in hospitals and the general population are known to be significantly influenced by drug interactions. ADR reduction is essential to ensuring hospitalized patients take their medications safely. Evidence suggests that even mild ADRs can significantly impact psychiatric patients due to strong relationships between drug-drug interactions, treatment failures, and higher healthcare costs due to avoidable medical complications.

Index Terms - Drug-drug interactions (haloperidol, lithium, diazepam etc..), psychiatry, Pharmacokinetics and Pharmacodynamics, Administration, Depressants, Central Nervous System, Gastro intestinal tract, Factors influencing drug interactions, Types of interactions.

INTRODUCTION

Drug- drug interactions occur when two or more medications are taken together, resulting in adverse effects, reduced efficacy or increased toxicity. Clinicians within the primary care setting are increasingly providing pharmacotherapy management of patients with psychiatric illness with over the 25% of primary care patients seeking care for major depression and 14% for schizophrenia [1,2] prescription for psychotropic medications have increased 48% with primary care providers [PCP] writing 65% and 80% of all anxiolytic and antidepressants prescriptions respectively - [3]. Schizophrenia [SCZ]treatment which include two groups; typical and atypical. SCZ Patients have multiple comorbidities and coadministration of drugs is quite common this may result in adverse drug-drug interaction.

Clinically significant drug -drug interactions are defined as events in which the pharmacodynamic or pharmacokinetic characteristics of a drug are altered by accumulation of a second drug to the patient's medication regimen, which can result in increase of adverse reaction or of efficacy [4,5]. They are two types of DDI include pharmacokinetic interactions and pharmacodynamic interactions occur concomitantly administered medications share similar target sites of actions. Clinical significant pharmacodynamic DDI can produce extrapyramidal symptoms [EPS],central nervous system [CNS]depression ,seizures, serotonin syndrome and QT interval prolongation[6,7].Pharmacokinetic DDIs involve alteration of drugs absorption ,distribution, metabolism and elimination by the addition of a second drug resulting in a change of

the primary drug serum concentration and difficult to predict[8] .DDIs involving changes in absorption result of changes in physicochemical properties of primary drug. Passage of large number of drugs crossways the intestinal wall are controlled by transporter proteins these p-glycoprotein it determines blood concentration and bioavailability of many drugs.

DRUG INTERACTIONS WITH LITHIUM

Analysis of adverse drug reactions in hospitalized psychiatric patients found lithium to be the most common psychiatric medication involved in ADRs [9]. Lithium is not metabolized; interactions are through other mechanisms. Diuretics are contraindicated and angiotensin- converting enzyme inhibitors can be used cautiously with lithium as they can increase the lithium level leading to toxicity [10,11] Drugs that reduce renal elimination of lithium such as nonsteroidal anti-inflammatory medications, cyclooxygenase inhibitors type 2 and metronidazole can increase lithium levels as well [11,12]. Lithium toxicity has been reported when calcium channel blockers, methyldopa and carbamazepine are used along with lithium. Decreased lithium levels have been additional with acetazolamide, alkalizing agents, and xanthine's (aminophylline, dyphylline, and theophylline). Lithium can be used carefully with nephrotoxic medications such as cyclosporine. Finally, lithium may prolong the effects of neuromuscular blocking agents used in surgeries and ECT.[10]

DRUG INTERACTIONS WITH CANCER MEDICATIONS

Tamoxifen is a prodrug that requires CYP450 2D6 metabolism to become an active metabolite.
[13,14]. Although tamoxifen is metabolized through other CYP450 enzymes as well as 2D6,[13]. these metabolic routes fail to produce the necessary active metabolite. Bupropion, fluoxetine, and paroxetine are potent 2D6 inhibitors and citalopram, desvenlafaxine, duloxetine, escitalopram, fluvoxamine, risperidone, sertraline, clomipramine, diphenhydramine, doxepin, chlorpromazine, methadone, perphenazine and haloperidol are less potent 2D6 inhibitors. A retrospective analysis of breast cancer patients found a 1.9-fold increase in breast cancer recurrence rate in patients taking concomitant tamoxifen and potent 2D6 inhibiting medication[15]. Thus, it is best to avoid using 2D6 inhibiting medications with tamoxifen. [16]

MEDICATIONS THAT LOWER THE SEIZURE THRESHOLD

Medications can additively lower the seizure threshold. TCAs (especially clomipramine,) atypical antipsychotics (especially clozapine,) antidepressants (especially bupropion,) psychostimulants, narcotics, some immunosuppressants (e.g. cyclosporine, chlorambucil, prednisone), some antibiotics (e.g. isoniazid, lindane, metronidazole, nalidixic acid, penicillin's), oral hypoglycaemic agents, anticholinergics (e.g. dimenhydrinate, diphenhydramine, cyclizine, meclizine, scopolamine, trimethobenzamide), anticholinesterases and lithium may lower the seizure threshold.[17]

FIG NO 1: DRUG-DRUG INTERACTIONS

Pharmacokinetic Drug Interactions

Absorption:

psychiatry drug interaction resulting from impaired absorption are similar to those seen in medical medications. Atypical antipsychotic clozapine can develop significant constipation requires additional medication to resolve. Bulk laxative such as psyllium, magnesium- based antacids and lactose products may reduce the absorption of other dugs if administered at same time.

Gastro-intestinal absorption

The gastro intestinal tract and the effects of several drugs with functional activity on the digestive system, represent favourable conditions for the emergency of DDI that may alter the drug bioavailability.[18]
Absorption of a drug through the gastrointestinal mucosa. The first factor is change in gastric

PH. The majority of drugs orally administered requires, to be dissolved and absorbed a gastric PH between 2.5 and 3.

H2 antagonist(ranitidine), antacids (aluminium hydroxide and sodium bicarbonate) and PPI (omeprazole, esomeprazole, pantoprazole) the gastric PH lead to decrease in cefpodoxime bioavailability, facility the absorption of beta-blocker and tolbutamide.

Motility disorders represent the third factor involved in absorption DDIs. Drugs able to increase the gastric transit (metoclopramide, cathartic) can reduce the time of contact between drug mucosal area of absorption inducing a decrease of drug absorption (controlled-release preparation or entero-protected drugs).[19]

Metabolism:

The CYP enzyme family plays a dominant the biotransformation of wide range number of drugs. Drug metabolism and these belong to families 1-4 but only 6 out of 30 isoforms belongs to family CYP1,2 and 3(CYP1A2,3A4,2C9,2C19,2D6 and 2E1) involved in the hepatic drug metabolism [22,23,24,25].

Recently, we documented in patient with epilepsy a DDI between phenobarbital and lamotrigine that induced the development of leukopenia and thrombohematologic.

Inhibitory Effect of Newer Antidepressants on CYP450 Isoenzymes [20]

Drug	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Citalopram	0	0	0	0	0
Fluoxetine	1	2	1 or 2	3	1 or 2
Fluvoxamine	3	2	3	1	2
Mirtazapine	0	0	0	1	0
paroxetine	1	1	1	3	1
sertraline	1	1	1	1 or 2	1
venlafaxine	0	0	0	1	1

TABLE 1: Inhibitory effects of newer antidepressants on CYP450 isoenzymes

Distribution:

Drugs are transported through a binding to plasma and tissues proteins. plasma proteins interacting with drugs, the risk for protein-binding interaction occurs unbound free fraction of competing increases more metabolism. Albumin, glycoprotein, lipoproteins. Unbound drug is available for passive diffusion to extravascular or tissue sites and typically determines drug concentration at the active site and its efficacy. Albumin represents the most prominent protein in plasma, it is synthesized in the liver and distributed in both plasma and extracellular fluids of skin, muscle and various tissues. Intestinal fluid albumin concentration is about 60% of that in plasma binding site (warfarin, benzodiazepines, digoxin). [26]

Phenytoin, valproic acid, diazepam tiagabine, as well as anti-psychotics including clonazepam, olanzapine.

Elimination:

Psychiatric drug interaction that results in altered elimination are rare. An increase in lithium levels can develop over 5to days after adding on NSAIDS, & Levels can return to baseline serum concentration within 7 days of stopping the NSAID. In case suggested ACE inhibitor & ARBs, it has been suggested that agents the lithium clearance. Excretion interaction primarily involve changes in renal excretion this might be due to drug induced reduction in glomerular filtration rate.

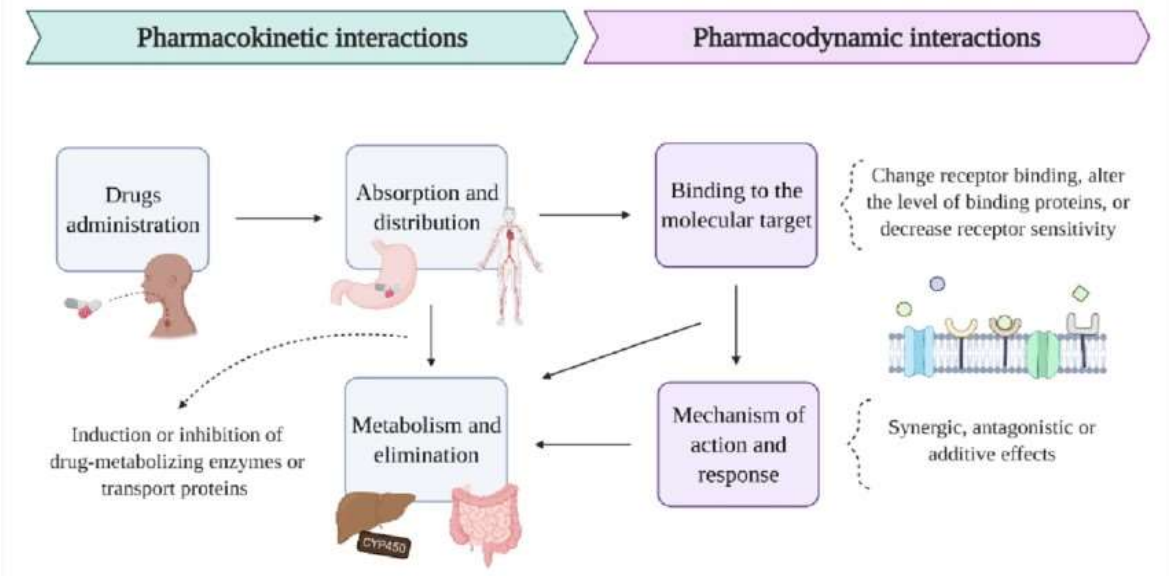

Fig no 2: Pharmacokinetics interactions and pharmacodynamics interactions

Pharmacodynamics Drug- Drug interactions

Pharmacodynamic drug-drug interactions occur when drugs being added to the antipsychotic compete at the receptor level, interfering with the therapeutic efficacy or perhaps contributing to an adverse effect. For example, when levodopa, a drug used for Parkinsonism with agonistic action at dopamine D_2 receptor is added, the antipsychotic through its dopamine antagonism can oppose the effects of levodopa. The result may culminate in worsening motor function, a relapse of psychosis or a combination thereof. PD interactions resulting in antagonistic, additive, or synergistic effects most often leading to adverse effects but, at times, rarely and deliberately augmented to obtain a favorable effect. drug-drug interactions occur when drugs act at the same or interrelated receptor sites, resulting in additive, synergistic, or antagonistic effects of each drug at the target receptor. Pharmacodynamic interactions, which result in a potentiation of the pharmacologic effects at the receptor, can be very important clinically. Most pharmaco-dynamic interactions are fairly straightforward and predictable if the practitioner has a basic understanding of the drug mechanism of action and receptor effects; therefore, the interactions can be anticipated, avoided, or managed when the combination is medically required. [27]

Anticholinergic Intoxication*:* The synergistic anticholinergic effect of drugs such as tricyclic antidepressants administered concurrently with antiparkinsonian agents can increase the anticholinergic effects of antipsychotics such as clozapine, olanzapine, and quetiapine, leading to dry mouth, blurred vision, and possibly delirium. [28] Amitriptyline taken concurrently with benztropine can produce pronounced constipation, heat stroke, urinary retention, and other shared side effects with exaggerated intensity.

Serotonin Syndrome*:* The neurotransmitter serotonin is involved in multiple bodily processes including aggression, pain, appetite, depression, and migraine. Potentially fatal, serotonin syndrome is caused by an increase in the amount of serotonin action in the CNS. Research has determined that overstimulation of the 5-HT_{2A} receptor appears to be substantially responsible for this reaction. The serotonin (5-HT_{1A}) receptor also contributes through a pharmacodynamic interaction in which increased synaptic concentration of a serotonin agonist saturates all receptor sites, thus magnifying the sum of serotonergic action. Drug categories that should be considered in this possible interaction include antidepressants, opioids, CNS stimulants, 5-HT_1 agonists (triptans), dextromethorphan, and certain herbal products available OTC (e.g., St. John's wort).[29]

Blood Dyscrasias*:* Almost all classes of psychotropic agents have been reported to cause blood dyscrasias. Leukopenia, neutropenia, thrombocytopenia, eosinophilia, anaemia, agranulocytosis, and altered platelet function are some of the hematologic side effects that may be encountered with psychiatric medication therapy. Clozapine is well known as a drug that causes dyscrasias; however, many other agents, including olanzapine, antidepressants, mood stabilizing AEDs (e.g., divalproex), and other atypical antipsychotics can cause similar problems.[30]

Other Issues: Coadministration of many antipsychotic agents (such as olanzapine concomitantly administered with conventional agents such as haloperidol or with atypical agents such as lurasidone) may increase the risk of adverse effects such as neuroleptic malignant syndrome (NMS) or seizures and/or can

result in the addition of other more common adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, and extrapyramidal symptoms.

Types of drug interactions

>Drug-gene treatment

>Drug-Food interactions

>Drug-allergy interactions

>Drug-Disease interactions

>Drug-Laboratory interactions

>Drug-drug interactions **Fig no: 3**. Types of drug interaction

Drug-Disease interactions

Medication may secondarily alter the body's processes such that normal physiologic pathways are altered indirectly for other drugs. For example, in the case of lithium, a patient's renal function may be sufficiently decreased as an adverse effect of NSAIDs, resulting in decreased lithium excretion and increased risk of toxicity. Diseases that are associated with organ function decline, including hepatic and renal compromise, are responsible for drug-disease interactions. Among the more notable drug-disease interactions reported in the 2019 American Geriatrics Society Beers Criteria is that occurring with the use of thiazolidinediones (pioglitazone, rosiglitazone) in patients with heart failure, due to the increased risk of fluid retention and/or exacerbation of heart failure.

Drug-Gene Interactions

The recognition of genetic variation influencing drug interactions has increased significantly. Medication efficacy can be affected by pharmacogenomic variations, with the most common association translating into increased risk of toxicity due to insufficient metabolism. The alternative risk, suboptimal efficacy due to genetically enhanced metabolism, is emerging as a factor potentially responsible for treatment resistance and failure.

Studies demonstrating improved outcomes through identification of genetically inappropriate medications are limited and continue to spark controversy. An exception is a randomized, controlled trial that evaluated the impact of using a pharmacogenomic test compared with treatment as usual. Gredenetal. looked at patients who were taking genetically inappropriate medications ("incongruent") at baseline and were switched. These patients experienced greater symptom improvement (33.5% versus 21.1%; P = .002), response (28.5% versus

16.7%; P = .036), and remission (21.5% versus 8.5%; P = .007) compared with those who remained on genetically incongruent regimens. Pharmacogenetic assessments include testing for genes that encode the CYP450 metabolizing enzymes so that treatment can be made based on the patient's genetic profile.

Drug-Food Interactions Drug-food interactions result from combining medication with food that interferes with the desired outcome. Although certain medications must be taken on an empty stomach due to impaired absorption, others cannot be taken with specific foods. The latter is the case with monoamine oxidase inhibitors that must also include an avoidance of foods that contain tyramine to prevent a potential hypertensive crisis.

Food-drug interactions include drug chelation of certain antibiotics with dairy products, which result in the preferential binding of the antibiotic to the chelating agent and inadequate systemic absorption. Additional interactions include pharmacodynamic intensification of ACE inhibitor–induced hyperkalaemia with a diet rich in potassium, or the metabolic consequence of hepatic inhibition precipitated by grapefruit, and increased adverse effects of certain statin drugs. Prescribers must be vigilant in assessing the risk of the patient's diet and current use of nutraceuticals and complementary/alternative medications, which have grown in popularity.

Understanding drug-food interactions is critical to minimizing unexpected adverse drug events.

Drug-Laboratory Interactions

Drug lab test interactions which effect the interactions which effect the result of normal lab report due to presence of one or more drug which can be cause of interference. Lab test, pt medical history and physical examination are vital components for a diagnosis, screening and management of disease lab test can be influenced in sensitivity and specificity by drugs consumed by patients whenever a drug lab interaction is observed in a clinical setting should be discussed in medical community to avoid possible error in diagnosis.

Drug-Allergy Interactions

Medications are one of our most powerful weapons against germs and diseases. But sometimes when people take medications, they can have an allergic reaction. That's when a drug causes the body's immune system to overreact. When that happens, they may not be able to use the drug again without risking more serious consequences. Any drug can cause an allergy. But some are more likely to than others. Antibiotics and certain painkillers are among the more common ones. The antibiotic penicillin is the drug most often reported to cause allergic reaction.

The possible drug-drug interactions in psychiatric patient

S.No	Drug-Drug Interactions	Type of Reactions	Interactions
1	Amisulpride + Haloperidol	Major	Increased risk of serious ventricular arrhythmia such as torsade de points
2	Ibuprofen + Prednisolone	Major	It may increase risk of gastrointestinal ulcer (or) bleeding.
3	Haloperidol + Sertraline	Major	Increased QT interval prolongation.
4	Alprazolam + Promethazine	Major	CNS depressant may result increased risk of respiratory.
5	Promethazine- Risperidone	Major	It may increase risk of QT interval.
6	Haloperidol +Diazepam	Major	Depressant may result increased risk of CNS depression.
7	Lorazepam +Olanzapine	Major	Result in potential of excessive sedation and cardiorespiratory depression.
8	Olanzapine + Diazepam	Moderated	Increased risk CNS depression, Orthostatic, Hypotension and excessive sedation.
9	Promethazine HCL + Trihexyphenidyl HCL	Major	Increased risk of urinary retention and sever constipation leading to paralytic illus.
10	Haloperidol + Trihexyphenidyl	Moderated	Excessive anticholinergic effects.

11	Olanzapine +Trihexyphenidyl	Moderated	Increased sever gastrointestinal adverse reaction.
12	Haloperidol + Olanzapine	Major	Increased risk of QT interval prolongation increased risk of CNS depression.
13	Lithium + Risperidone	Moderated	It may result in weakness dyskinesia and increased extra pyramidal symptom brain damage.
14	Haloperidol + Risperidone	Major	Increased risk of QT interval prolongation.
15	Amisulpride + Escitalopram	Major	Increased risk of serious ventricular arrhythmia.
16	Escitalopram + Lithium	Minor	These drugs increased in result in risk of serotonin syndrome.
17	Baclofen + Diazepam	Major	Increased risk of CNS depression.
18	Diazepam + Quetiapine fumarate	Minor	Increased CNS depressant.
19	Fluoxetine + Olanzapine	Major	Increased risk of QT interval prolongation.
20	Pregabalin +Amitriptyline	Major	Increased effect of other by synergism.
21	Baclofen + Amitriptyline	Moderated	Increased sedation and result in memory loss (amnesia) or loss of muscle tone.
22	Lurasidone +Oxcarbazepine	Major	It reduced exposure of lurasidone.
23	Buspirone HCL + Lithium citrate	Major	It Increased of serotonin syndrome.
24	Clonazepam + Gabapentin	Major	Increased risk of hypoventilation.
25	Escitalopram + propranolol	Major	Increased CYP2D6 substrate exposure.

Table No 3: Types of drug-drug interactions

1.*Amisulpride + Haloperidol (Major)*

MONITOR CLOSELY: Haloperidol can cause dose-related 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 arrhythmias including torsade de pointes and sudden death. Haloperidol treatment alone has been associated with a number of reported cases of torsade de pointes and sudden death. 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., hypokalaemia, hypomagnesemia). The extent of drug-induced QT prolongation is dependent on the particular drug(s) involved and dosage(s) of the drug(s). In addition, certain agents with anticholinergic properties (e.g., sedating antihistamines; antispasmodics; neuroleptics; phenothiazines; skeletal muscle relaxants; tricyclic antidepressants) may have additive parasympatholytic and central nervous system-depressant effects when used in combination with haloperidol. Excessive parasympatholytic effects may include paralytic ileus, hyperthermia, mydriasis, blurred vision, tachycardia, urinary retention, psychosis, and seizures. MANAGEMENT: Caution is recommended if haloperidol is used in combination with other drugs that can prolong the QT interval, particularly when administered intravenously or at higher than recommended dosages. Haloperidol is not approved by the FDA for intravenous administration. Patients should be advised to seek prompt medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, light headedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope. 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. Patients should be advised to notify their physician promptly if they experience potential symptoms of anticholinergic intoxication such as abdominal pain, fever, heat intolerance, blurred vision, confusion, and/or hallucinations. Ambulatory patients should be counselled 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. [31,32,33]

2.*Ibuprofen + Prednisolone*

MONITOR: The combined use of corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the potential for serious gastrointestinal (GI) toxicity, including inflammation, bleeding, ulceration, and perforation. In a large, case-control study of elderly patients, those who used corticosteroids and NSAIDs concurrently had an estimated relative risk (RR) for peptic ulcer disease and GI haemorrhage of 14.6 compared to those who used neither. Corticosteroid use was associated with a doubling of the risk (estimated RR = 2.0), but the risk was confined to those who also used NSAIDs. It is possible that both categories of agents are ulcerogenic and have additive effects on the GI mucosa during coadministration. Some investigators have also suggested that the primary effect of corticosteroids in this interaction is to delay healing of erosions caused by
NSAIDs rather than cause de novo ulcerations.

MANAGEMENT: Caution is advised if corticosteroids and NSAIDs are used together, especially in patients with a prior history of peptic ulcer disease or GI bleeding and in elderly and debilitated patients. During concomitant therapy, patients should be advised to take the medications with food and to immediately report signs and symptoms of GI ulceration and bleeding such as severe abdominal pain, dizziness, light headedness, and the appearance of black, tarry stools. The selective use of prophylactic anti-ulcer therapy (e.g., antacids, H2- antagonists) may be considered. [34,35,36]

3.***Haloperidol + Sertraline***

MONITOR CLOSELY: Haloperidol can cause dose-related 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 arrhythmias including torsade de pointes and sudden death. Haloperidol treatment alone has been associated with a number of reported cases of torsade de pointes and sudden death. 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., hypokalaemia, hypomagnesemia). The extent of drug-induced QT prolongation is dependent on the particular drug(s)

involved and dosage(s) of the drug(s). In addition, certain agents with anticholinergic properties (e.g., sedating antihistamines; antispasmodics; neuroleptics; phenothiazines; skeletal muscle relaxants; tricyclic antidepressants) may have additive parasympatholytic and central nervous system-depressant effects when used in combination with haloperidol. Excessive parasympatholytic effects may include paralytic ileus, hyperthermia, mydriasis, blurred vision, tachycardia, urinary retention, psychosis, and seizures.

MANAGEMENT: Caution is recommended if haloperidol is used in combination with other drugs that can prolong the QT interval, particularly when administered intravenously or at higher than recommended dosages. Haloperidol is not approved by the FDA for intravenous administration. Patients should be advised to seek prompt medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, light headedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope. 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. Patients should be advised to notify their physician promptly if they experience potential symptoms of anticholinergic intoxication such as abdominal pain, fever, heat intolerance, blurred vision, confusion, and/or hallucinations. Ambulatory patients should be counselled 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.[37]

*4.**Alprazolam + Promethazine***

MONITOR: Central nervous system- and/or respiratory-depressant effects may be additively or synergistically 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.

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 counselled to avoid hazardous activities requiring mental alertness and motor coordination until they know how these agents affect them, and to notify their physician if they experience excessive or prolonged CNS effects that interfere with their normal activities.[38]

*5.**Promethazine + Risperidone***

MONITOR: Agents with anticholinergic properties (e.g., sedating antihistamines; antispasmodics; neuroleptics; phenothiazines; skeletal muscle relaxants; tricyclic antidepressants; disopyramide) may have additive effects when used in combination. Excessive parasympatholytic effects may result in paralytic ileus, hyperthermia, heat stroke, and the anticholinergic intoxication syndrome. Peripheral symptoms of intoxication commonly include mydriasis, blurred vision, flushed face, fever, dry skin and mucous membranes, tachycardia, urinary retention, and constipation. Central symptoms may include memory loss, disorientation, incoherence, hallucinations, psychosis, delirium, hyperactivity, twitching or jerking movements, stereotypy, and seizures. Central nervous system-depressant effects may also be additively or synergistically increased when these agents are combined, especially in elderly or debilitated patients. Use of neuroleptics in combination with other neuroleptics or anticholinergic agents may increase the risk of tardive dyskinesia. In addition, some neuroleptics and tricyclic antidepressants may cause prolongation of the QT interval and theoretically, concurrent use of two or more drugs that can cause QT interval prolongation may result in additive effects and increased risk of ventricular arrhythmias including torsade de pointes and sudden death.

MANAGEMENT: Caution is advised when agents with anticholinergic properties are combined, particularly in the elderly and those with underlying organic brain disease, who tend to be more sensitive to the central anticholinergic effects of these drugs and in whom toxicity symptoms may be easily overlooked. Patients should be advised to notify their physician promptly if they experience potential symptoms of anticholinergic intoxication such as abdominal pain, fever, heat intolerance, blurred vision, confusion, and/or hallucinations. Ambulatory patients should be counselled 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. [39,40]

*6.**Haloperidol + Diazepam***

MONITOR: Central nervous system- and/or respiratory-depressant effects may be additively or synergistically 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.

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 counselled to avoid hazardous activities requiring mental alertness and motor coordination until they know how these agents affect them, and to notify their physician if they experience excessive or prolonged CNS effects that interfere with their normal activities.[38]

7.***Lorazepam + Olanzapine***

MONITOR CLOSELY: CNS- and/or cardiorespiratory-depressant effects may be increased during concomitant use of olanzapine and benzodiazepines, especially in elderly or debilitated patients. In clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than in placebo-treated patients (3.5% vs. 1.5%). 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: Caution is necessary when olanzapine is used in combination with benzodiazepines. Ambulatory patients should be made aware of the possibility of additive CNS effects and counselled to avoid activities requiring mental alertness until they know how these agents affect them. They should also be advised to avoid rising abruptly from a sitting or recumbent position and to contact their physician if they experience symptoms of hypotension such as dizziness, light headedness, or fainting. 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. [41,42]

*8.**Olanzapine + Diazepam***

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*9.**Promethazine HCL + Trihexyphenidyl***

MONITOR: Agents with anticholinergic properties (e.g., sedating antihistamines; antispasmodics; neuroleptics; phenothiazines; skeletal muscle relaxants; tricyclic antidepressants; disopyramide) may have additive effects when used in combination. Excessive parasympatholytic effects may result in paralytic ileus, hyperthermia, heat stroke, and the anticholinergic intoxication syndrome. Peripheral symptoms of intoxication commonly include mydriasis, blurred vision, flushed face, fever, dry skin and mucous membranes, tachycardia, urinary retention, and constipation. Central symptoms may include memory loss, disorientation, incoherence, hallucinations, psychosis, delirium, hyperactivity, twitching or jerking movements, stereotypy, and seizures. Central nervous system-depressant effects may also be additively or synergistically increased when these agents are combined, especially in elderly or debilitated patients. Use of neuroleptics in

combination with other neuroleptics or anticholinergic agents may increase the risk of tardive dyskinesia. In addition, some neuroleptics and tricyclic antidepressants may cause prolongation of the QT interval and theoretically, concurrent use of two or more drugs that can cause QT interval prolongation may result in additive effects and increased risk of ventricular arrhythmias including torsade de pointes and sudden death.
MANAGEMENT: Caution is advised when agents with anticholinergic properties are combined, particularly in the elderly and those with underlying organic brain disease, who tend to be more sensitive to the central anticholinergic effects of these drugs and in whom toxicity symptoms may be easily overlooked. Patients should be advised to notify their physician promptly if they experience potential symptoms of anticholinergic intoxication such as abdominal pain, fever, heat intolerance, blurred vision, confusion, and/or hallucinations. Ambulatory patients should be counselled 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.[40]

*10.**Haloperidol + Trihexyphenidyl***

MONITOR: Centrally-acting anticholinergic agents may antagonize the therapeutic effects of neuroleptic agents. Although these drugs have been used together clinically, the possibility of increased risk of adverse effects such as central nervous system depression and tardive dyskinesia should also be considered. In addition, excessive anticholinergic effects may occur in combination use, which can result in paralytic ileus, hyperthermia, heat stroke, and the anticholinergic intoxication syndrome. Peripheral symptoms of anticholinergic intoxication commonly include mydriasis, blurred vision, flushed face, fever, dry skin and mucous membranes, tachycardia, urinary retention, and constipation. Central symptoms may include memory loss, disorientation, incoherence, hallucinations, psychosis, delirium, hyperactivity, twitching or jerking movements, stereotypy, and seizures. In hot weather, the risk of hyperthermia and heat stroke should be considered, as neuroleptic agents can interfere with temperature regulation in the hypothalamus while anticholinergic agents tend to inhibit peripheral sweating mechanisms.

MANAGEMENT: Caution is advised if anticholinergic agents are used with neuroleptic agents, particularly in the elderly and those with underlying organic brain disease, who tend to be more sensitive to the central anticholinergic effects of these drugs and in whom toxicity symptoms may be easily overlooked. Prophylactic administration of anticholinergic agents is sometimes given clinically during neuroleptic therapy for drug-induced parkinsonism or extrapyramidal symptoms but may not always be appropriate. Patients prescribed this combination should be advised to notify their physician promptly if they experience potential symptoms of anticholinergic intoxication such as abdominal pain, fever, heat intolerance, blurred vision, confusion, and hallucinations. Ambulatory patients should be counselled to avoid activities requiring mental alertness until they know how these agents affect them. A dosage reduction in one or both drugs may be necessary if excessive adverse effects develop. During hot weather, patients should avoid prolonged sun exposure and intense physical exertion and maintain adequate fluid intake.[43]

*11.**Olanzpine + Trihexyphenidyl***

MONITOR: Centrally-acting anticholinergic agents may antagonize the therapeutic effects of neuroleptic agents. Although these drugs have been used together clinically, the possibility of increased risk of adverse effects such as central nervous system depression and tardive dyskinesia should also be considered. In addition, excessive anticholinergic effects may occur in combination use, which can result in paralytic ileus, hyperthermia, heat stroke, and the anticholinergic intoxication syndrome. Peripheral symptoms of anticholinergic intoxication commonly include mydriasis, blurred vision, flushed face, fever, dry skin and mucous membranes, tachycardia, urinary retention, and constipation. Central symptoms may include memory loss, disorientation, incoherence, hallucinations, psychosis, delirium, hyperactivity, twitching or jerking movements, stereotypy, and seizures. In hot weather, the risk of hyperthermia and heat stroke should be considered, as neuroleptic agents can interfere with temperature regulation in the hypothalamus while anticholinergic agents tend to inhibit peripheral sweating mechanisms.
MANAGEMENT: Caution is advised if anticholinergic agents are used with neuroleptic agents, particularly in the elderly and those with underlying organic brain disease, who tend to be more sensitive to the central anticholinergic effects of these drugs and in whom toxicity symptoms may be easily overlooked. Prophylactic administration of anticholinergic agents is sometimes given clinically during neuroleptic therapy for drug-induced parkinsonism or extrapyramidal symptoms but may not always be appropriate. Patients prescribed this combination should be advised to notify their physician promptly if they experience potential symptoms of anticholinergic intoxication such as abdominal pain, fever, heat intolerance, blurred vision, confusion, and

hallucinations. Ambulatory patients should be counselled to avoid activities requiring mental alertness until they know how these agents affect them. A dosage reduction in one or both drugs may be necessary if excessive adverse effects develop. During hot weather, patients should avoid prolonged sun exposure and intense physical exertion and maintain adequate fluid intake. [40,44]

*12.**Haloperidol + Olanzapine***

MONITOR: In general, the concurrent use of multiple neuroleptic agents may increase the risk of adverse effects such as sedation, orthostatic hypotension, and extrapyramidal symptoms due to overlapping pharmacodynamic activities. In one case report, the combination of haloperidol and olanzapine was associated with severe parkinsonism in an elderly patient with a history of bipolar disorder. Prior to the addition of olanzapine, the patient had been stabilized on haloperidol and exhibited mild symptoms of parkinsonism that were controlled with benztropine. While hospitalized, a decision was made to switch from haloperidol to olanzapine in an attempt to minimize the parkinsonism. Over the next 7 days, olanzapine dosage was gradually increased while haloperidol dosage simultaneously decreased. The patient developed increased rigidity, mumbling speech, and inability to walk, which did not resolve until 3 days after the cessation of haloperidol. Benztropine was then discontinued, and symptoms did not recur while the patient was maintained on olanzapine alone.

MANAGEMENT: The use of multiple neuroleptic agents should be approached with caution. Patients should be monitored closely and advised to notify their physician if they experience excessive sedation, orthostasis, or extrapyramidal symptoms (e.g., dystonic reactions, akathisia, parkinsonism, neuroleptic malignant syndrome, tardive dyskinesia).

*13.**Lithium + Risperidone***

MONITOR: Coadministration of lithium with neuroleptic agents, particularly haloperidol, has been associated with rare cases of an encephalopathic syndrome characterized by weakness, lethargy, fever, tremors, confusion, extrapyramidal symptoms, leucocytosis, and elevated liver enzymes and blood urea nitrogen. This syndrome may be similar to, or the same as, neuroleptic malignant syndrome. Other, more common central nervous system effects may also be increased, such as dizziness, drowsiness, confusion, difficulty concentrating, and impairment in thinking, judgment, and motor coordination.

MANAGEMENT: Close monitoring for central nervous system adverse effects is recommended when lithium is used with neuroleptic agents. Dosage adjustments or discontinuation of one or both drugs may be necessary if an interaction is suspected. [44,45]

*14.**Haloperidol + Risperidone***

MONITOR CLOSELY: Haloperidol can cause dose-related 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 arrhythmias including torsade de pointes and sudden death. Haloperidol treatment alone has been associated with a number of reported cases of torsade de pointes and sudden death. 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., hypokalaemia, hypomagnesemia). The extent of drug-induced QT prolongation is dependent on the particular drug(s) involved and dosage(s) of the drug(s). In addition, certain agents with anticholinergic properties (e.g., sedating antihistamines; antispasmodics; neuroleptics; phenothiazines; skeletal muscle relaxants; tricyclic antidepressants) may have additive parasympatholytic and central nervous system-depressant effects when used in combination with haloperidol. Excessive parasympatholytic effects may include paralytic ileus, hyperthermia, mydriasis, blurred vision, tachycardia, urinary retention, psychosis, and seizures.

MANAGEMENT: Caution is recommended if haloperidol is used in combination with other drugs that can prolong the QT interval, particularly when administered intravenously or at higher than recommended dosages. Haloperidol is not approved by the FDA for intravenous administration. Patients should be advised to seek prompt medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, light headedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope. 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. Patients should be advised to notify their physician promptly if they experience potential symptoms of anticholinergic intoxication such as abdominal pain, fever, heat intolerance, blurred vision, confusion, and/or hallucinations. Ambulatory patients should be counselled 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.

15. ***AMISULPRIDE + ESCITALOPRAM***

MONITOR CLOSELY: Escitalopram can cause dose-dependent prolongation of the QT interval. Theoretically, coadministration with other agents that can prolong the QT interval including tricyclic antidepressants and other antidepressants (e.g., trazodone) may result in additive effects and increased risk of ventricular arrhythmias such as torsade de pointes and sudden death. In a double-blind, placebo-controlled ECG study consisting of 113 healthy subjects, the change from baseline in QTc (Fridericia-corrected) was 4.3 msec for escitalopram 10 mg/day and 10.7 msec for the supratherapeutic dosage of 30 mg/day. Based on the established exposure-response relationship, the predicted QTc change from placebo under the C max for 20 mg/day is 6.6 msec. Cases of QT interval prolongation and torsade de pointes have been reported during post marketing use. 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., hypokalaemia, hypomagnesemia). Also, the extent of drug-induced QT prolongation is dependent on the particular drug(s) involved and dosage(s) of the drug(s).

MANAGEMENT: In general, the concomitant use of multiple serotonergic agents should be avoided if possible, or otherwise approached with caution if potential benefit is deemed to outweigh the risk. Patients should be closely monitored for symptoms of the serotonin syndrome during treatment. Particular caution is advised when increasing the dosages of these agents. If serotonin syndrome develops or is suspected during the course of therapy, all serotonergic agents should be discontinued immediately and supportive care rendered as necessary. 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 and may require sedation, neuromuscular paralysis, intubation, and mechanical ventilation in addition to the other measures. Due to the potential for additive effects on the QT interval, ECG monitoring may also be appropriate when escitalopram is used with tricyclic antidepressants or other antidepressants like trazodone. Patients should be advised to seek prompt medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, light headedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope.[46]

*16.**Escitalopram + Lithium***

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 arrhythmias including torsade de pointes and sudden death. In a double-blind, placebo-controlled ECG study consisting of 113 healthy subjects, the change from baseline in QTc (Fridericia-corrected) was 4.3 msec for escitalopram 10 mg/day and 10.7 msec for the supratherapeutic dosage of 30 mg/day. Based on the established exposure-response relationship, the predicted QTc change from placebo under the C max for 20 mg/day is 6.6 msec. Cases of QT interval prolongation and torsade de pointes have been reported during post marketing use. 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., hypokalaemia, hypomagnesemia). 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. Patients should be advised to seek prompt medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, light headedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope. When escitalopram is used in combination with other drugs that cause CNS and/or respiratory depression, patients should be monitored for potentially excessive or prolonged CNS and respiratory depression. Ambulatory patients should be counselled to avoid hazardous activities requiring mental alertness and motor coordination until they know how these agents affect them, and to notify their doctor if they experience excessive or prolonged CNS effects that interfere with their normal activities.

*17.**Baclofen + Diazepam***

MONITOR: Central nervous system- and/or respiratory-depressant effects may be additively or synergistically 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.

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 counselled to avoid hazardous activities requiring mental alertness and motor coordination until they know how these agents affect them, and to notify their physician if they experience excessive or prolonged CNS effects that interfere with their normal activities.[47]

*18.**Diazepam + Quetiapine furamide***

MONITOR: Central nervous system- and/or respiratory-depressant effects may be additively or synergistically 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.

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 counselled to avoid hazardous activities requiring mental alertness and motor coordination until they know how these agents affect them, and to notify their physician if they experience excessive or prolonged CNS effects that interfere with their normal activities.

*19.**Fluoxetine + Olanzapine***

MONITOR: It is uncertain whether olanzapine causes clinically significant prolongation of the QT interval. In pooled studies of adults as well as pooled studies of adolescents, there were no significant differences between olanzapine and placebo in the proportion of patients experiencing potentially important changes in ECG parameters, including QT, QT cF (Fridericia-corrected), and PR intervals. In clinical trials, clinically meaningful QTc prolongations (QT cF >=500 msec at any time post-baseline in patients with baseline QT cF <500 msec) occurred in 0.1% to 1% of patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo. Published studies have generally reported no significant effect of olanzapine on QTc interval, although both QTc prolongation and QTc shortening have also been reported. There have been a few isolated case reports of QT prolongation in patients receiving olanzapine. However, causality is difficult to establish due to confounding factors such as concomitant use of drugs that cause QT prolongation and underlying conditions that may predispose to QT prolongation (e.g., hypokalaemia, congenital long QT syndrome, preexisting conduction abnormalities).

MANAGEMENT: Some authorities recommend caution when olanzapine is used with drugs that are known to cause QT prolongation. ECG monitoring may be advisable in some cases, such as in patients with a history of cardiac arrhythmias or congenital or family history of long QT syndrome. Patients should be advised to seek prompt medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, light headedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope.

20.Pregabaline + Amitriptyline

MONITOR: Central nervous system- and/or respiratory-depressant effects may be additively or synergistically 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.

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 advised to avoid hazardous activities requiring mental alertness and motor coordination until they know how these agents affect them, and to notify their physician if they experience excessive or prolonged CNS effects that interfere with their normal activities.[47]

*21.**Baclofen + Amitriptyline***

MONITOR: Using amitriptyline together with baclofen may increase side effects such as dizziness, drowsiness, confusion, and difficulty concentrating. Some people, especially the elderly, may also experience impairment in thinking, judgment, and motor coordination. You should avoid or limit the use of alcohol while being treated with these medications. Also avoid activities requiring mental alertness such as driving or operating hazardous machinery until you know how the medications affect you. Talk to your doctor if you have any questions or concerns. It is important to tell your doctor about all other medications you use Central nervous system- and/or respiratory-depressant effects may be additively or synergistically 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.

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 counselled to avoid hazardous activities requiring mental alertness and motor coordination until they know how these agents affect them, and to notify their physician if they experience excessive or prolonged CNS effects that interfere with their normal activities.

*22.**Lurasidone + Oxcarbazepine***

MONITOR: Central nervous system- and/or respiratory-depressant effects may be additively or synergistically 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.

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 agents affect them, and to notify their physician if they experience excessive or prolonged CNS effects that interfere with their normal. [48,49]

*23.**BuspironeHcl + Lithium Citrate***

MONITOR: Concomitant administration of lithium with serotonergic drugs (e.g., selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, triptans (5-HT1 agonists), buspirone, fentanyl, St. John's wort, tramadol, tryptophan) or drugs that impair metabolism of serotonin (e.g., monoamine oxidase inhibitors) can precipitate serotonin syndrome, which is a rare but serious and potentially fatal condition thought to result from hyperstimulation of brainstem 5-HT1A and 2A receptors. Symptoms of the serotonin syndrome may include mental status changes such as irritability, altered consciousness, confusion, hallucination, 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 diarrhoea. MONITOR: Central nervous system (CNS) depressant effects may be additively or synergistically 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 be potentiated.

MANAGEMENT: Close monitoring for potential serotonin toxicity and excessive CNS depression is advised when lithium is used with other serotonergic agents or monoamine oxidase inhibitors. Particular caution is advised when increasing the dosages of these agents. Patients should be counselled to avoid hazardous activities requiring mental alertness and motor coordination until they know how these agents affect them, and to notify their physician if they experience excessive or prolonged CNS effects that interfere with their normal activities. If serotonin syndrome develops or is suspected during the course of therapy, all serotonergic agents should be discontinued immediately and supportive care rendered as necessary. 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 and may require sedation, neuromuscular paralysis, intubation, and mechanical ventilation in addition to the other measures. [50,51]

24.***CLONAZEPAM + GABA PENTENE***

MONITOR: Central nervous system- and/or respiratory-depressant effects may be additively or synergistically 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.

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 agents affect them, and to notify their physician if they experience excessive or prolonged CNS effects that interfere with their normal activities.

MONITOR: Central nervous system- and/or respiratory-depressant effects may be additively or synergistically 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.[47]

*25.**Escitalopram + Propranolol***

MONITOR: Partial clinical data recommend that careful serotonin reuptake inhibitors (SSRIs) might potentiate the pharmacologic effects of some beta-blockers. There have been case reports of patients steadied on beta-blocker therapy who established bradycardia, hypotension, and wide-ranging heart block subsequent the whole of a SSRI, subsequently demanding discontinuation of one or both agents and/or organization of a enduring innovator. The contact is also corroborated by data from in vitro and clinical studies relating paroxetine and metoprolol directed by one group of investigators. The planned mechanism is SSRI inhibition (competitive and/or noncompetitive) of CYP450 2D6, the isoenzyme in control for the metabolic clearance of beta-blockers such as carvedilol, labetalol, metoprolol, nebivolol, propranolol, and timolol. Paroxetine and norfluoxetine (the active metabolite of fluoxetine), in exact, are potent inhibitors of CYP450 2D6 and may be more likely than other SSRIs to cause the interaction. On the further indicator, fluvoxamine is a potent inhibitor of CYP450 1A2 and may suggestively interact with propranolol, which is a substrate of both CYP450 2D6 and 1A2. MANAGEMENT: During associated remedy with SSRIs, a lower initial dosage and more careful titration of the beta-blocker may be proper. Cardiac function should be carefully monitored and the beta-blocker dosage adjusted accordingly, mainly following initiation, withdrawal or change of dosage of SSRI in patients who are stabilized on their beta-blocker treatment. Due to the long half-life of fluoxetine and its active metabolite, norfluoxetine, the risk of an interaction may exist for a prolonged period (up to several weeks) after withdrawal of fluoxetine. To avoid the interaction, use of beta-blockers that are primarily eliminated by the kidney such as atenolol, acebutolol, betaxolol, carteolol, and nadolol may be considered.

CONCLUSION:

The pharmacist can contribute significantly in educating the patients or their family members regarding DDIs, polypharmacy, ADRs, and assessing the patient medication history. This review was focused on representative DDIs between two drugs. there is a disparity between the potential and clinically relevant DDIs. Our study also helped to define the significant role of the pharmacist in assessing and controlling DDIs. Further research may include an evaluation of the economic, clinical, and humanistic outcomes of clinically important DDIs, especially among those at risk. Clinically significant drug interactions in psychiatry can have serious consequences on treatment outcomes and patients' safety. Awareness, understanding, and proactive management of drug interactions vital for optimizing psychiatric treatment. These may also alter the drug-drug interactions in psychiatry. However, there are major drug interactions which has been discussed and also includes moderate and minor interactions which cause sever effects.

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REFERENCES

1.Regier DA, Narrow WE, Rae DS, Manderscheid RW, Locke BZ, Goodwin FK. The de facto US mental and addictive disorders service system: Epidemiologic Catchment Area prospective 1-year prevalence rates of disorders and services. Archives of general psychiatry. 1993 Feb 1;50(2):85-94.

2.Barrett JE, Barrett JA, Oxman TE, Gerber PD. The prevalence of psychiatric disorders in a primary care practice. Archives of general psychiatry. 1988 Dec 1;45(12):1100-6.

3.Lieberman JA. The use of antipsychotics in primary care. Journal of Clinical Psychiatry. 2003 Mar 1; 5:3-8.

4.Ereshefsky L, Jhee S, Grothe D. Antidepressant drug-drug interaction profile update. Drugs in R & D. 2005 Nov; 6:323-36.

5.Johnson JA, Bootman JL. Drug-related morbidity and mortality and the economic impact of pharmaceutical care. American Journal of Health-System Pharmacy. 1997 Mar 1;54(5):554-8.

6. Yap KL, Tay WL, Chui WK, Chan A. Clinically relevant drug interactions between anticancer drugs and psychotropic agents. European journal of cancer care. 2011 Jan;20(1):6- 32.

7.Schellander R, Donnerer J. Antidepressants: clinically relevant drug interactions to be considered. Pharmacology. 2010 Sep 8;86(4):203-15.

8.Strain JJ, Chiu NM, Sultana K, Karim A, Caliendo G, Mustafa S, Strain JJ. Psychotropic drug versus psychotropic drug—update. General hospital psychiatry. 2004 Mar 1;26(2):87105.

9. Thomas M, Boggs AA, DiPaula B, Siddiqi S. Adverse drug reactions in hospitalized psychiatric patients. Annals of Pharmacotherapy. 2010 May;44(5):819-25.

10.Wolter Kluwer. Periodically cited 2013 oct 16.

11.Healthcare T. Micromedex Healthcare Series. Greenwood Village, Colo., Thomson Reuters Healthcare. 2011; 11:2018.

12. English BA, Dortch M, Ereshefsky L, Jhee S. Clinically significant psychotropic drug-drug interactions in the primary care setting. Current psychiatry reports. 2012 Aug; 14:376-90.

13.Hansten PD, Horn JR. The top 100 drug interactions: a guide to patient management. H & H Publications, LLP; 2004.

14.Oesterheld J.P450 Drug-Interactions Inhibitors Tablet's. Seattle:Genelex Corporationc2012(updated periodically; cited 2013 Oct 16).

15.Aubert RE, Stanek EJ, Yao J, Teagarden JR, Subar M, Epstein RS, Skaar TC, Desta Z, Flockhart DA. Risk of breast cancer recurrence in women initiating tamoxifen with CYP2D6 inhibitors. Journal of Clinical Oncology. 2009 Jun 20;27(18_suppl):CRA508-.

16.Binkhorst L, Mathijssen RH, van Herk-Sukel MP, Bannink M, Jager A, Wiemer EA, van Gelder T. Unjustified prescribing of CYP2D6 inhibiting SSRIs in women treated with tamoxifen. Breast cancer research and treatment. 2013 Jun;139:923-9.

17.Oh CY, Bainbridge J. Lowering the seizure threshold associated with antidepressants, stimulants, antipsychotics, and others. Mental Health Clinician. 2012 Nov 1;2(5):127-8.

18.Mantia G, Provenzano G. Rilevanza clinica delle interazioni farmacologiche di tipo farmacocinetico [Clinical significance of pharmacokinetic interactions]. ACTA MEDICA MEDITERRANEA. 2008;24(1):23-7.

19. Lee Ht, Lee Yj, Chung Sj, Shim Ck. Effect Of Prokinetic Agents, Cisapride And Metoclopramide, On The Bioavailability In Humans And Intestinal Permeability In Rats Of Ranitidine, And Intestinal Charcoal Transit In Rats. Research Communications In Molecular Pathology And Pharmacology. 2000 Nov 1;108(5-6):311-23.

20.Spina E, Scordo MG, D'Arrigo C. Metabolic drug interactions with new psychotropic agents. Fundamental & clinical pharmacology. 2003 Oct;17(5):517-38.

21. Sudlow Gd, Birkett Dj, Wade Dn. The Characterization Of Two Specific Drug Binding Sites On Human Serum Albumin. Molecular Pharmacology. 1975 Nov ;11(6):824-32.

22.Guengerich FP. Characterization of human cytochrome P450 enzymes. The FASEB Journal. 1992 Jan;6(2):745-8.

23.Nelson DR, Kamataki T, Waxman DJ, Guengerich FP, Estabrook RW, Feyereisen R, Gonzalez FJ, Coon MJ, Gunsalus IC, Gotoh O, Okuda K. The P450 superfamily: update on new sequences, gene mapping, accession numbers, early trivial names of enzymes, and nomenclature. DNA and cell biology. 1993 Jan;12(1):1-51.

24.Nebert Dw, Nelson Dr, Coon Mj, Estabrook Rw, Feyereisen R, Fujii- Kuriyama Yo, Gonzalez Fj, Guengerich Fp, Gunsalus Ic, Johnson Ef, Loper Jc. The P450 Superfamily: Update On New Sequences, Gene Mapping, And Recommended Nomenclature. Dna And Cell Biology. 1991 Jan;10(1):1-4.

25.Nakamura K, Goto F, Ray WA, McAllister CB, Jacqz E, Wilkinson GR, Branch RA. Interethnic differences in genetic polymorphism of debrisoquin and mephenytoin