# Psychopharmacology in Medically Ill Patients

8

Beena Nair

## Contents



## 8.1 Introduction

Appropriate use of psychopharmacology in the medically ill patients requires careful consideration of the risks and benefits of using these medications. This would involve careful assessment of the underlying medical condition, interaction of psychotropic medications with other medications used to treat medical problems, potential alterations to pharmacokinetics from the medical condition, and increased vulnerability to side effects from medications because of impaired hepatic, renal, cardiac, and gastrointestinal functioning.

This chapter focuses on:

- Understanding the principles of psychopharmacology
- Understanding the pharmacokinetic and pharmacodynamic drug–drug interactions
- Understanding the use of psychotropic medications in various medical conditions and organ failure
- Diagnosis and management of medical emergencies from the side effects of psychotropic medications including serotonin syndrome and neuroleptic malignant syndrome

B. Nair, MD (✉)
Associate Clinical Professor, UCSF-Fresno,
155N. Fresno St., Fresno, CA 93701, USA
e-mail: bnair@fresno.ucsf.edu

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## 8.2 Principles of Psychopharmacology in the CL Setting

1. Review patient's medical problems, laboratory findings, and imaging studies if available.
2. Review all inpatient and outpatient medications: psychotropics and non-psychotropics, over-the-counter medications, herbal medications and supplements, and determine whether these medications were actually taken.
3. Check for medications that could be contributing to patient's altered mental state like anticholinergic agents, opioids, and benzodiazepines.
4. Avoid polypharmacy: Consider lowering the dosage or discontinuing medications rather than adding new medications.
5. Use the minimum dose of medication necessary to obtain the desired response.
6. Determine past response to psychotropic medications.
7. Avoid prescribing medications to be given as needed (PRN). If as needed medications are required, monitor dosage and frequency of use.
8. Add or discontinue one drug at a time: simultaneous changes can make it difficult to determine efficacy and adverse drug reaction.
9. Use drug serum level if possible to check for toxicity and compliance.
10. Understand patients' psychosocial and financial background which could affect patient's compliance to medication.

## 8.3 Pharmacokinetics and Pharmacodynamics in the Medically Ill

Impaired hepatic, renal, cardiac, and gastrointestinal functioning can alter the absorption, metabolism, distribution, and excretion of the psychotropic medications.

### 8.3.1 Absorption

Absorption of a drug is influenced by the characteristics of the absorption site including surface area, pH, mucosal integrity and function, local blood flow and the chemical properties of the drug. The absorption of orally administered drugs can be altered by food, pH, chelating agents, gut flora changes, diseases, or other drugs affecting gastric or small bowel function. Absorption of intramuscular injections is dependent on muscle mass and tissue perfusion.

### 8.3.2 Distribution

Distribution of a drug is influenced by serum pH, blood flow, protein binding, lipid solubility, and the degree of ionization. This could be altered in cardiac, hepatic, and renal impairments.

### 8.3.3 Elimination

The majority of psychotropic drugs are eliminated by hepatic metabolism and a few by renal clearance. The hepatic clearance of drugs can be affected in liver disease. In conditions like cirrhosis there is decreased hepatic blood flow that will affect the rate of delivery of the drug to the liver. There is also decrease in the intrinsic metabolic capacity of enzymes which will result in impaired metabolism and clearance of the drug. Renal clearance of drugs can be affected in kidney failure. Dose adjustment by starting low and slowly titrating up is required in these situations.

### 8.3.4 Metabolism

Drug metabolism in the liver is divided into two phases: *Phase I* reaction involves oxidation, reduction, and hydrolysis. These processes tend to increase water solubility of the drug and can generate metabolites that are chemically active and potentially toxic. Cytochrome P450 enzymes are the major enzymes involved in the Phase I

metabolism. They consist of a closely related family of 50 isoforms; six of them metabolize 90 % of drugs with the two most significant enzymes being CYP3A4 and CYP2D6 (Lynch and Price 2007). *Phase II* reaction involves glucuronidation, acetylation, and sulfation (conjugation pathway). UGTs (uridine glucuronosyltransferases) are the important enzymes, mainly 2B7. Chemically active Phase I products are rendered relatively inert and suitable for elimination by Phase II.

### 8.3.5 Drug–Drug Interactions (DDI)

Understanding the use of psychotropic medication in the medically ill patients requires understanding of drug–drug interactions at pharmacokinetic and pharmacodynamic levels. Most interactions go unreported because they are mild or unrecognized. DDI can have significant clinical implications when using medications with a narrow therapeutic index, when there is a serious adverse drug reaction, and when treatment is ineffective. It can result in considerable patient morbidity and mortality (Sandson et al. 2005).

#### 8.3.5.1 Pharmacokinetic DDI

Pharmacokinetic DDI through alteration in metabolism can result in either induction of metabolism, which will result in decrease in the drug level, or inhibition of metabolism, which will increase the drug level. The third way is through the polymorphic nature of enzymes which results in fast metabolizers or slow metabolizers.

Examples of potent inhibitors of P450 are fluoxetine (2D6, 2C9), paroxetine (2D6, 2B6), fluvoxamine (1A2, 2C19), sertraline (dose dependent 2D6, potent inhibitor of UGT 1A4), nafazodone (3A4), bupropion (2D6), duloxetine (2D6), haloperidol (2D6), cimetidine (all-cyp450), ciprofloxacin (1A2), fluconazole (2C9), ketoconazole (3A4), erythromycin (3A4), isoniazid (2C19), diltiazem (3A4), grape fruit juice (1A2, 3A4), omeprazole (2C19), most protease inhibitors (3A4), quinidine (2D6), diphenhydramine (2D6), valproic acid (2C9), ritonavir (2C9, 2C19, 2D6, 3A4) (Lynch and Price 2007; Sandson et al. 2005).

Examples of potent inducers of P450 are rifampin, carbamazepine, phenobarbital, phenytoin, St. John's Wort, chronic smoking.

Examples of pharmacokinetic DDI include:

Carbamazepine (3A4 inducer) and ethinyl estradiol containing contraceptive: this can reduce estradiol level and lead to failure of contraception (Crawford et al. 1990).

Fluoxetine, paroxetine (2D6 inhibitor) and Risperidone: this can increase risperidone level and increase the risk for adverse extrapyramidal effects (Spina et al. 2002).

#### 8.3.5.1.1 Pharmacodynamic DDI

Pharmacodynamic DDI involves interaction of drugs at the intended site of action. This may be additive, synergistic, or antagonistic. Classic examples of pharmacodynamic interactions include that between a monoamine oxidase inhibitor and a serotonin reuptake inhibitor, resulting in serotonin syndrome, and that between a tricyclic antidepressant and an anticholinergic agent like benztropine, causing anticholinergic toxicity. Pharmacodynamic DDI is easier to anticipate, recognize and avoid.

## 8.4 Pharmacogenomics

Drug efficacy and toxicity vary substantially across individuals. Clinical consequences may include a prolonged time to optimal therapy and in some cases, serious adverse events.

Various factors may influence the variability of drug effects, including age, liver function, concomitant diseases, nutrition, smoking, and drug–drug interactions and inherited polymorphisms in genes coding for drug metabolizing enzymes, drug receptors, drug transporters and molecules involved in signal transduction. Genetics may account for 20–95 % of variability in drug disposition and effects (Evans and McLeod 2003).

It may be possible to predict therapeutic failures or severe adverse drug reactions in

individual patients by testing for important DNA polymorphisms (genotyping) in genes related to the metabolic pathway (pharmacokinetics) and in genes related to signal transduction pathway (pharmacodynamics) (Phillips et al. 2001).

There is pronounced ethnic variability in the population distribution of metabolizer types for a given CYP enzyme. For example: less than 1 % of Asians, 2–5 % of African-Americans, and 6–10 % of Caucasians are poor metabolizers of CYP2D6 (Bradford 2002). The presence of the HLA-B*1502 allele is associated with carbamazepine-induced Stevens-Johnson syndrome (SJS) and/or toxic epidermal necrolysis (TEN) (Chung et al. 2004).

## 8.5 Alternate Routes of Administration

In medically complicated patients who are either agitated and refusing to take oral medication or are intolerant of oral dosing of psychiatric medication because of nausea, vomiting, nothing by mouth restrictions, aspiration risk, difficulty swallowing, post oro-maxillary surgery, or physiologically incapable of intestinal absorption (because of gastric or bowel dysfunction or resection), there is clinical dilemma. These situations require alternate routes to administer psychotropic medications (Thompson and DiMartini 1999). Using alternate routes like intravenous (IV), intramuscular (IM), sublingual (SL), and rectal route bypasses the effect of first-pass metabolism and can cause a significant increase in bioavailability of the drug. The parenteral route (IM/IV) is used to sedate highly anxious or agitated patients. For patients with severe muscle atrophy and poor tissue perfusion, such as in cardiac insufficiency, IM injections should be avoided. Poor venous access, infiltration and infection can complicate IV use. Some antipsychotics like chlorpromazine, haloperidol, droperidol, ziprasidone, olanzapine, aripripazole and benzodiazepines like lorazepam are available in IM forms. Haloperidol can be used IV with 40 % improved bioavailability compared to oral administration (Chang et al. 1992) and with less extrapyramidal side effects (Menza et al. 1987) but patients should be on a cardiac monitor because of the increased risk of QTc prolongation and torsade de pointes if high doses are used. Similarly lorazepam can be used IV in severely agitated and anxious patients but the patient should be monitored for respiratory depression. The only mood stabilizer available in parenteral form (IV) is valproate sodium.

Depot antipsychotics are administered intramuscularly. Their rate limiting step is the release of the medication from the depot solution which is dependent on the amount of subcutaneous fat. Sublingual form may be an effective route, especially for nonionized, highly lipid-soluble medications. Haloperidol, chlorpromazine, clomipramine, diazepam, nitrazepam, promethazine, and trihexyphenidyl are examples of nonionized, highly lipophilic drugs that may diffuse across the mucosal membranes at physiologic pH (pH 7.4) Mirtazapine, olanzapine, and asenapine are available in sublingual forms. For patients with severe nausea any oral stimulation is intolerable and may not benefit from this form. In addition, many medications have a bitter taste, causing further nausea (Thompson and DiMartini 1999). Selegiline is available in a transdermal patch as an antidepressant. Selected benzodiazepines like lorazepam can be given in IM/IV/Sublingual, intranasal, intrathecal, and rectal routes.

## 8.6 The Elderly

Elderly patients have slower absorption, metabolism and elimination of drugs. The distribution of the drugs can be affected by impaired hepatic, renal, and cardiac functioning. The elderly will be more sensitive and susceptible to side effects of medications. It is very important to start psychotropic medications at a lower dose and titrate the dose slowly monitoring for side effects. Also drugs with anticholinergic properties like tricyclic antidepressants and benzodiazapines should be avoided to reduce the risk of fall.

## 8.7 Psychopharmacology in Organ Diseases

### 8.7.1 Hepatic Disease

Liver disease is highly prevalent in patients with psychiatric illness and comorbid substance use disorder. The liver is responsible for a number of physiological processes including synthesis of proteins and clotting factors and the metabolism of drugs and other substances. Abnormal liver function can cause physical and psychiatric symptoms including abnormal blood clotting, ascites, variceal bleeding, muscle wasting, fatigue, personality changes, psychomotor dysfunction, affective symptoms, cognitive impairment including impaired memory, concentration, and reaction time, and in severe cases, coma. In patients with end stage liver disease psychiatric symptoms emerge not only from the underlying organ failure but also from the stress of dealing with a terminal illness (Crone et al. 2006).

Liver disease can affect medication pharmacokinetics from absorption to metabolism, to distribution and elimination. This can affect the drug level, duration of action and increase the risk for adverse effects. In cirrhosis, synthesis of plasma protein is altered. This can affect the protein binding of drugs resulting in higher levels of free pharmacologically active drugs. There is impaired metabolism and elimination of drugs because of reduced synthesis of liver enzymes and decreased blood flow to the liver. Most psychotropics are lipid soluble and undergo extensive phase I hepatic metabolism. Only a few psychotropics are dependent on renal clearance including lithium, gabapentin, and topiramate. Phase I enzymes (cytochrome P450 isoenzyme families), which are centrally located in the portal triad, are mainly affected in cirrhosis, whereas Phase II metabolism (mainly glucuronidation) is preserved in cirrhosis (Pacifici et al. 1990). Choosing a psychotropic drug that mainly uses the phase II pathway for metabolism (lorazepam, temazepam, and oxazepam) may be useful in patients with cirrhosis (Crone et al. 2006). Sedatives should be used with caution in liver failure because they can precipitate hepatic encephalopathy (Häussinger 2010).

When using psychotropic drugs in patients with liver disease the severity of the disease and therapeutic index of the drug should be carefully considered to avoid drug toxicity and side effects.

Hepatotoxicity is a known rare side effect of some psychotropics including nafazodone, duloxetine, valproic acid, and carbamazepine. They are either relatively contraindicated in patients with preexisting liver disease or should be used with extreme caution. Minor elevations in transaminases are common and usually benign. Elevation of AST or ALT levels of 2–3 times the baseline is significant. Low platelets from liver failure can increase the risk of bleeding when using drugs like valproic acid that can cause thrombocytopenia.

Drugs like tricyclic antidepressants and low potency antipsychotics that have significant anticholinergic effects may exacerbate hepatic encephalopathy in cirrhotics secondary to intestinal stasis and central effects (Levenson 2005).

Prophylactic administration of SSRIs to patients with hepatitis C has been found to significantly lower the incidence of interferon-induced major depression when compared with placebo in a meta-analysis, and the SSRIs were well tolerated (Jiang et al. 2014).

Lithium is renally excreted but its level could fluctuate in patients with end stage liver disease with ascites because of the fluctuating fluid balance.

Haloperidol in low dose remains the most commonly chosen antipsychotic for psychosis and agitation associated with hepatic encephalopathy (Prabhakar and Bhatia 2003).

The rule of thumb is to reduce the initial dose of medication and titrate the dose slowly for drugs primarily metabolized by the liver. Choose drugs with wide therapeutic index and monitor for side effects.

### 8.7.2 Renal Disease

Subsyndromal depression is seen in about 25 % of individuals with end stage renal disease (ESRD) and major depression in 5–22 % of this

population (Cohen et al. 2004). Anxiety, substance use disorders, delirium, and dementia are also common psychiatric conditions in this population.

Most psychotropic medications are well tolerated and efficacious in the treatment of patients with ESRD and renal insufficiency. End stage renal disease may affect the pharmacokinetics of the drugs. The Physician's Desk Reference generally recommends that patient with ESRD be administered *two-thirds the usual or maximum dose of most psychotropic drugs.*

In ESRD, excess urea may affect the absorption of medications by gastric alkalinizing and by changes in gastrin levels. A cachetic person has less fluid and less body mass and a decreased volume of distribution resulting in higher concentration of medication. The patient with ascites and edema has a higher volume of distribution and may require higher initial doses of medication. Patients with renal failure often have decreased amount of albumin. Also, retention of urea and other substances that compete for plasma protein binding sites will result in a higher free fraction of plasma protein bound drug like valproic acid. The greater the protein binding of a medication, the lower the dose required in renal failure. Drug metabolites that are pharmacologically active may be retained in patients with renal insufficiency and may cause adverse effects.

In a review of psychotropic medication use in renal disease (Cohen et al. 2004), SSRIs are beneficial in ESRD. Excretion of fluoxetine and sertraline is unchanged in ESRD, plasma concentration of paroxetine is increased in renal impairment and a starting dose of 10 mg is recommended. Venlafaxine and Mirtazapine have active metabolites and their clearance is reduced by 50 % in renal disease. Bupropion has active metabolites that are completely excreted through the kidney. The metabolites may accumulate in dialysis patients and predispose these patients to seizures. Less than 1 % of haloperidol is excreted in the urine and it appears to be a safe medication to use in ESRD. With risperidone, wide variation in clearance is noted between poor and extensive metabolizers. Clearance of the sum of risperidone and its metabolite 9-hydroxy risperidone is reduced by 60 % in renal failure (Heykants et al. 1994). Antipsychotics that prolong QTc like thioridazine and ziprasidone are best avoided in ESRD because of risk of life threatening arrhythmias with electrolyte shifts. Benzodiazepines are metabolized in the liver and dose reduction is generally not necessary. The half-life of lorazepam may be prolonged in ESRD (Wagner and O'Hara 1997). Lithium is contraindicated in acute renal failure but not in chronic renal failure patients on dialysis. Lithium is completely dialyzed and can be given as a single dose post hemodialysis.

### 8.7.3 GI Diseases

Psychotropic drugs with anticholinergic properties should be avoided in patients with gastroparesis and constipation. Antidepressants, when used to treat concomitant mood disorders in inflammatory bowel disease, have been shown to reduce relapse rates, use of steroids, and endoscopies (Goodhand et al. 2012). TCAs have been found to be effective in controlling symptoms in irritable bowel syndrome (Rahimi et al. 2009).

Gastrointestinal side effects are common with initiation of SSRIs and may be undesirable in patients with increased gastric motility or diarrhea. There are reports of prolonged bleeding time, ecchymosis, purpura, epistaxis, gastrointestinal, genitourinary, postoperative, and intracranial bleeding in patients receiving SSRIs. Serotonin plays a role in hemostasis. Platelets release serotonin in response to vascular injury. Serotonin binds to receptors on adjacent platelets and contributes to platelet aggregation. SSRIs inhibit about 90 % of the activity of serotonin transporter in platelets. Decreased serotonin in platelets may increase the risk of abnormal bleeding (Bismuth-Evenzal et al. 2012; de Abajo et al. 2006).

There are multiple studies relating the use of SSRIs with upper gastrointestinal bleeding (Dalton et al. 2003; Andrade et al. 2010). Older age, a history of gastrointestinal problems, and concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) are identified as risk factors. Increased gastric acidity and gastric

erosion in conjunction with an SSRI could also contribute to increased risk for bleeding. For patients with a previous history of upper-gastrointestinal bleeding or peptic ulcer, and for those who take NSAIDs, oral anticoagulants, antiplatelet drugs, or corticosteroids, the addition of an acid-suppressing agent to SSRI may reduce the risk of bleeding (de Abajo and García-Rodríguez 2008). The risk of abnormal bleeding is associated with the degree of serotonin reuptake inhibition by antidepressants. Antidepressants with a higher degree of inhibition of serotonin reuptake have 2.6 times the risk of bleeding compared with antidepressants with a low degree of serotonin reuptake inhibition (Meijer et al 2004).

### 8.7.4 Cardiovascular Disease

Depression is highly prevalent in patients with cardiovascular disease and is independently associated with poor prognosis (Joynt et al. 2003). Among individuals with established ischemic heart disease, depression has been found to be associated with an approximately threefold to fourfold increase in the risk of subsequent cardiovascular morbidity and mortality (Zellweger et al. 2004)

Depressed patients are more likely to eventually develop cardiovascular disease and also have a higher mortality rate than the general population. There is a graded relationship: the more severe the depression, the higher the subsequent risk of mortality and other cardiovascular events (Hare et al. 2013). Between 31–45 % of patients with coronary artery disease (CAD) suffer from clinically significant depressive symptoms (Celano and Huffman 2011). Fifteen to twenty percent of patients with coronary artery disease meet criteria for MDD at any given time (Carney and Freedland 2008).

Depression is associated with changes in an individual's health status which may influence the development and course of cardiovascular disease, including noncompliance with medical treatment, increased presence of cardiovascular risk factors like smoking and hypertension, physiological changes including nervous system activation, cardiac rhythm disturbances, systemic and localized inflammation, and hypercoagulability (Joynt et al. 2003).

Sertraline is considered safe and effective in patients with recurrent depression post MI. It has been found to reduce the incidence of severe cardiac events (death, myocardial infarction, congestive heart failure, stroke, and recurrent angina ("SADHART" study, Glassman et al. 2002).

Psychotropic medications can cause adverse cardiovascular effects including tachycardia, orthostatic hypotension, conduction disturbances, and arrhythmias. TCAs and low potency antipsychotics block alpha1 receptors which can cause postural hypotension resulting in syncope and fall.

Tricyclic antidepressants are contraindicated after myocardial infarction because of their cardiotoxic side effects including QTc prolongation, postural hypotension, anticholinergic effects, and conduction delays (Bilgi and Campbell 1979). Venlafaxine can cause hypertension in higher doses (Mbaya et al. 2007).

Studies on the cardiac effects of lithium indicate high frequency of electrocardiographic T wave morphology changes especially nonspecific T-wave flattening. Therapeutic and toxic levels of lithium have infrequently been associated with sinus node dysfunction or sinoatrial block, atrioventricular conduction disturbances and the appearance or aggravation of ventricular irritability and premature ventricular contractions (Mitchell and Mackenzie 1982; Mohandas and Rajmohan 2007). The effects are more profound during lithium intoxication. The incidence of cardiac complications may increase with age. Higher lithium concentration has been correlated with prolonged QTc (Mamiya et al. 2005). Lithium should be used with caution in patients with congestive heart failure because of salt restriction and diuretic therapy.

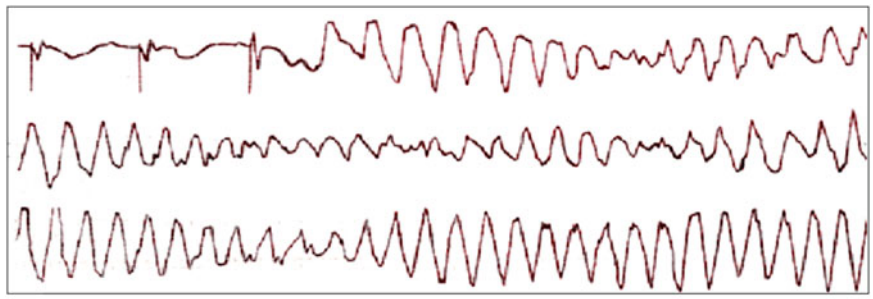
Methylphenidate is well tolerated in the medically ill, the terminally ill, and older adults. Most studies indicate about 5 and 30 % patients develop some adverse effects on methylphenidate. These are usually mild and resolve with discontinuation of medication (Hardy 2009). The most common side effects reported are agitation or restlessness, sinus tachycardia or palpitations, delirium or

confusion, and insomnia. Both hypertension and hypotension have been reported in older adults on methylphenidate, which are relatively infrequent. One serious uncommon adverse effect is arrhythmia, which is reversible with discontinuation of the medication. In 2007, the FDA required new warnings in psychostimulant labeling regarding reports of serious cardiovascular events, including sudden death, stroke, and myocardial infarction in children and adults using stimulants for attention deficit hyperactivity disorder.

Both typical and atypical antipsychotics have a similar, dose-related increased risk of sudden cardiac death (Ray et al. 2009).

#### 8.7.4.1 Psychotropics and QTc

Psychotropic drugs can delay cardiac repolarization and prolong the rate-corrected QT interval (QTc). A prolonged QTc can be followed, in rare cases, by the life-threatening polymorphic ventricular tachyarrhythmia called torsade de pointes (TdP)



*Torsade de pointes*

There are individual and environmental risk factors for QTc prolongation including age over 65 years, female sex (longer QTc interval than men and twice the risk of drug-induced TdP), preexisting cardiovascular disease, congenital long QT syndrome (Jervell and Lange-Nielsen syndrome ), bradycardia (sinus bradycardia, second and third -degree atrioventricular block) and electrolyte disturbances (hypokalemia, hypomagnesemia). High plasma concentrations of the offending drug from overdose, rapid infusion of the drug, inhibition of drug metabolism by concomitantly administered drugs, and/or reduced drug clearance due to renal or hepatic insufficiency can also increase the risk for QTc prolongation (Wenzel-Seifert et al. 2011).

TdP typically presents as dizziness, seizures, and syncope. It can lead to ventricular fibrillation and sudden cardiac death. Prolonged QTc interval at baseline has been shown to be a risk factor for drug induced QT prolongation and life threatening arrhythmia (Shouten et al. 1991). Drugs that prolong the QT interval bind to cardiac potassium channels ($I_{Kr}$, also known as HERG channels). The resulting blockade of potassium efflux from cardiomyocytes prolongs the repolarization phase. In the congenital long-QT syndrome a mutation of the $I_{Kr}$ gene causes prolongation of the QT interval.

There is considerable intra-individual variability of QTc. In a given individual QTc can vary from 76 to 102 millisecond (ms) over the course of 24 h (Wenzel-Seifert et al. 2011). In normal persons, the mean QTc length is roughly 400 ms. The upper limit of normal is defined as 460 ms for women, and 450 ms for men. A QTc interval >500 ms is considered to be a major risk factor for the development of TdP.

Among psychotropic medications thioridazine and ziprasidone have the highest risk of QTc prolongation (Wenzel-Seifert et al. 2011; Beach et al. 2013). Clinically significant risk is associated with haloperidol given intravenously in high doses. QTc prolongation has been reported with newer antipsychotic drugs (mainly quetiapine, risperidone, olanzapine, clozapine), most of the tricyclic and tetracyclic antidepressants, selective monoamine reuptake inhibitors—citalopram, fluoxetine, paroxetine, venlafaxine, and lithium. The risk of pathological QTc prolongation

increases with the dose. Thioridazine, pimozide, sertindole, droperidol, and IV haloperidol have been documented to cause torsade de pointes and sudden death. There is no documented association with olanzapine, quetiapine, or risperidone and sudden death (Glassman and Bigger 2001). There are case reports of ziprasidone causing Tdp especially in overdose (Heinrich et al. 2006; Manini et al. 2007).

Individual risk in each patient should be carefully considered. Factors that can help to reduce the risk includes checking EKG for QTc before treatment in high risk patients, slow dose escalation in cases of altered elimination or inhibited metabolism, regular EKG monitoring of patients at high risk and those taking additional medications that can prolong the QTc interval, monitoring serum potassium and potential electrolyte loss in patients with vomiting, diarrhea, diuretic therapy, and eating disorders, and administration of magnesium sulfate if the QTc is markedly prolonged (Wenzel-Seifert et al. 2011). Discontinue psychotropic medication if the QTc is longer than 500 ms, Use alternate medication for agitation like benzodiazepines or anticonvulsants until QTc returns to normal.

## 8.7.5 Neurological Conditions

### 8.7.5.1 Cerebrovascular Disease

Patients with cerebrovascular disease are sensitive to the CNS side effects of psychotropic medications. Psychotropic drugs causing postural hypotension like TCAs and low potency typical antipsychotics should be avoided in patients with syncopal episodes. SSRIs are preferred in post-stroke depression. Studies on use of SSRIs on post stroke patients have shown improvement in global cognitive functioning, specifically in verbal and visual memory functions (Jorge et al 2010) and decrease in dependence, disability, neurological impairment, anxiety, and depression (Mead et al. 2012).

SSRI exposure is associated with an increased risk of intracerebral and intracranial hemorrhage especially in combination with anticoagulants (Hackam and Mrkobrada 2012).

All antipsychotics—typical and atypical—are associated with an increased risk of stroke when used in elderly demented patients (Gill et al. 2005; Douglas and Smeeth 2008).

### 8.7.5.2 Epilepsy

The prevalence of depression in patients with epilepsy ranges from 20 to 30 % in community samples to 50 to 55 % in epilepsy clinics (Jackson and Turkington 2005) with a 4–5 times increased risk of suicide in this population (Matthews and Barabas 1981).

All antidepressants and antipsychotics are known to lower seizure threshold. Seizure incidence rate ranges from approximately 0.1–1.5 % in patients treated with a therapeutic dose of these medications compared to the general population rate of 0.07–0.09 %. In overdose, the seizure risk increases to 4–30 % (Pisani et al. 2002). It is a dose-dependent adverse effect.

Risk factors for seizures include individual factors like inherited seizure threshold, history of seizures, brain injury, older age, and reduced drug clearance. Medication risk factors include higher dose, rate of upward titration of medication and sudden drug withdrawal. To reduce risk for seizures it is important to evaluate for these factors and start medication at a low dose with a slow escalation avoiding complex drug combinations (Pisani et al. 2002).

Psychotropic drugs with the highest seizure risk include bupropion, maprotiline, and clomipramine among antidepressants, and chlorpromazine and clozapine among antipsychotics. Antidepressants with lower seizure risk include phenelzine, tranylcypromine, fluoxetine, paroxetine, sertraline, trazadone, and venlafaxine. Fluphenazine, haloperidol, pimozide, and risperidone are among antipsychotics with the lowest seizure risk (Pisani et al. 2002).

### 8.7.5.3 Parkinson's Disease (PD)

Neuropsychiatric symptoms are common in PD including depression, anxiety, apathy, fatigue, and cognitive impairment. Medications used for the treatment of PD can cause psychiatric symptoms including delusions, hallucinations, manic symptoms, impulsive behaviors, and agitation.

These symptoms can affect the quality of life and daily functioning and place the patient at increased risk for nursing home placement. Depressive symptoms are present in 30–40 % of PD patients and 40 % of patients have anxiety symptoms (Aarsland et al. 2009).

Most antidepressants have been reported to be effective and well tolerated when used to treat depression and anxiety symptoms in PD. SSRIs can potentially have interaction with monoamine oxidase inhibitors used to treat PD like selegiline, with increased risk for serotonin syndrome. Benzodiazepines should be used with caution as they can increase the risk for falls and worsen cognitive, autonomic, and sleep related problems (Aarsland et al. 2009).

Apathy and fatigue are common symptoms in patients with Parkinson's disease and can contribute significantly to disability. Apathy is seen in 17–70 % of patients with PD. Prevalence of fatigue is about 32–58 % which may predate the onset of motor symptoms and increase over time. Medications used to treat these symptoms have limited evidence of efficacy, including dopamine agonists, psychostimulants, and modafinil (Aarsland et al. 2009).

Psychotic symptoms occur frequently in patients with PD and may be accompanied by affective and behavioral symptoms. Conventional antipsychotics are not recommended for use in patients with PD, as they have been reported to significantly worsen the motor symptoms of PD. Clozapine has been shown to be effective for the treatment of psychosis in PD without aggravation of parkinsonian symptoms (Eng and Welty 2010). Even a low dose of clozapine, 50 mg or less, can significantly improve drug induced psychosis without worsening parkinsonism (The Parkinson study group 1999). Quetiapine has been frequently used to treat psychosis in PD and has shown some efficacy in open label trials, even though placebo controlled studies have shown conflicting results. One comparative study with clozapine showed no statistically significant difference in effectiveness compared to quetiapine (Shotbolt et al. 2010). Olanzapine has worsened parkinsonian symptoms in three trials (Weintraub and Hurtig 2007).

### 8.7.6 Diabetes Mellitus

Serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine) provide benefit both for depression and diabetic neuropathic pain (Goldstein et al. 2005; Sindrup et al. 2005; Zin et al. 2008). TCAs can also help with the neuropathic pain but patients may be more vulnerable to the anticholinergic side effects, postural hypotension, and sexual dysfunction.

Use of atypical antipsychotics in diabetes should be weighed against the risk of metabolic syndrome with these drugs including weight gain, glucose intolerance, new onset type 2 diabetes mellitus, diabetic ketoacidosis, and hyperlipidemia. Clozapine and olanzapine have the highest risk and should be avoided in diabetics (Jin et al. 2004).

### 8.7.7 Psychotropics and the Syndrome of Inappropriate Release of Antidiuretic Hormone (SIADH)

Antidiuretic hormone (ADH) induces water retention in the distal tubule and collecting duct of the nephron. SIADH involves sustained release of ADH from the posterior pituitary or enhanced action of ADH on the kidneys. Increased ADH activity impairs kidney's ability to dilute urine resulting in decreased excretion of ingested water and concentrated urine. If fluid intake is not reduced serum hypotonicity and hyponatremia will occur. Patient will present with normal volume status (euvolemia) because the excess water distributes evenly throughout the body's fluid compartments. Common symptoms of SIADH include weakness, lethargy, headache, anorexia, and weight gain. Severe cases present with confusion, convulsions, coma, and death. The early symptoms are vague and nonspecific, and may mimic symptoms of psychiatric disorder (Spigset and Hedenmalm 1995).

SIADH is reported with all class of psychotropics except lithium, which was used in the past to treat SIADH. Risk factors for SIADH and

hyponatremia with psychotropics include concomitant use of thiazide diuretics, female gender, older age, low BMI, first few weeks of treatment, polypharmacy, CYP3A4 interactions, basal low levels of sodium (hyponatremia), and hyperkalemia (Wilkinson et al. 1999; Madhusoodanan et al. 2002; Spigset and Hedenmalm 1997). There are a large number of reports of SIADH and hyponatremia associated with SSRI use, with the incidence varying from 0.5 to 32 % (Jacob and Spinler 2006). In a review of reported cases of hyponatremia and SIADH associated with SSRIs, fluoxetine was involved in about 75 % of the cases, paroxetine in about 12 %, sertraline and fluvoxamine in about 11 % of the cases. The median time to onset of hyponatremia was 13 days (range 3 to 120 days). Most (83 %) of the published cases involved patients 65 years of age or more (Liu et al. 1996). Elderly patients should be monitored closely in the first 4 weeks of SSRI therapy for clinical signs suggestive of hyponatremia.

Treatment of SIADH includes discontinuation of the offending drug, restriction of fluid intake, and in severe cases may require infusion of sodium chloride. If continued treatment with an antidepressant or antipsychotic is indicated, a drug with a different pharmacological profile should be chosen, and the serum sodium levels should be monitored closely. If treatment with the drug that caused SIADH must be continued, concomitant treatment with demeclocycline may reduce the tendency to hyponatremia.

### 8.7.8 Respiratory Illness

The prevalence of clinical anxiety ranges from 10 to 55 % among patients with COPD (Willgoss and Yohannes 2013). Prevalence of depressive symptoms is 2.5 times greater for patients with severe COPD than controls (van Manen et al. 2002).

Antidepressants (SSRIs and SNRIs) are indicated as first line agents for treating depression and anxiety in COPD patients. Benzodiazepines can significantly reduce the ventilatory response to hypoxia. This may precipitate respiratory failure in a patient with marginal respiratory reserve. Patients with severe bronchitis ("blue bloaters"), severe restrictive lung disease, and sleep apnea are most vulnerable to the adverse effects of benzodiazepines. Antipsychotics in small doses are safer alternatives to benzodiazepines for treating acute anxiety in COPD but their potential neurological and cardiovascular side effects should be considered before use in medically ill patients. Non-pharmacological interventions like cognitive behavior therapy, pulmonary rehabilitation, relaxation therapy, and palliative care have shown to reduce depression and anxiety and improve quality of life in patients with COPD (Cafarella et al. 2012; Mikkelsen et al. 2004).

## 8.8 Psychotropic Drug Induced Medical Emergencies

### 8.8.1 Neuroleptic Malignant Syndrome (NMS)

NMS is a rare, idiosyncratic, life threatening complication of treatment with antipsychotic drugs. It is characterized by fever, severe muscle rigidity, autonomic dysfunction, and mental status changes. Recent data suggest an incidence of 0.01–0.02 % (Stubner et al. 2004). NMS remains a significant source of morbidity and mortality (10 %) in patients on antipsychotics if unrecognized and untreated.

Risk factors associated with increased incidence of NMS include agitation, dehydration, restraint, preexisting brain pathology, malnutrition, and iron deficiency (Rosebush et al. 1991). In 15–20 % of cases a prior episode of NMS is described (Caroff and Mann 1993). Pharmacologic variables that increase the risk include exposure to drugs that block dopamine D2 receptors. NMS has been reported in non-psychiatric patients treated with dopamine antagonists like prochlorperazine and metoclopramide. Withdrawal of dopaminergic agents like L-dopa can precipitate NMS like reaction. High potency conventional antipsychotics are associated with the greatest risk compared to low potency and atypical antipsychotics. Higher dosage and rapid dose escalation, depot neuroleptics, and more

than one antipsychotic (33 % increased risk) are other factors found to increase the risk for NMS (Keck et al. 1989).

#### 8.8.1.1 Clinical Features

The signs and symptoms useful to make the diagnosis of NMS include recent exposure to dopamine antagonists, or dopamine agonist withdrawal; hyperthermia >100.4 °F or >38.0 °C on at least two occasions; rigidity; mental status alteration; creatine kinase elevation at least four times the upper limit of normal; sympathetic nervous system lability; tachycardia plus tachypnea; and a negative workup for other causes (Gurrera et al. 2011).

*Clinical Course*: Onset is related to the initiation of neuroleptic treatment. Progression of symptoms is usually insidious over days. There are occasional cases of fulminant onset within hours of drug administration. Alteration in mental status and other neurological signs precede systemic signs in more than 80 % of cases of NMS (Velamoor et al. 1994).

Laboratory investigations are essential to rule out other disorders or complications. Abnormal laboratory findings seen in NMS, although not specific for the diagnosis, include elevated creatine phosphokinase (CPK), leukocytosis, elevated transaminases, and low serum iron.

Complications include metabolic acidosis, respiratory failure, irreversible brain damage, pulmonary embolus, electrolyte disturbances, coagulopathy, rhabdomyolysis, and renal failure.

Once NMS is diagnosed and oral antipsychotic drugs are discontinued, it is self-limited in most cases. The mean recovery time after drug discontinuation is about 7–10 days. The duration of NMS episode may be prolonged when long acting depot antipsychotics are implicated.

Risk factors for increased mortality include older age, higher temperatures, depot neuroleptics, preexisting brain pathology, and development of renal failure.

### 8.8.1.2 Management of NMS

Early diagnosis and discontinuation of the offending agent including antipsychotics, lithium, and all dopamine blocking agents including antiemetics, and initiating supportive medical therapy is the mainstay in the management of NMS. Supportive measures include serial monitoring of CPK and electrolytes, aggressive volume resuscitation, physical cooling measures for extreme hyperthermia, and antihypertensives or pressors for autonomic instability. Intensive medical care should include careful monitoring for complications including cardiorespiratory failure, renal failure, aspiration pneumonia, and coagulopathies. Benzodiazepines do not have a preventive effect but they may ameliorate symptoms and hasten recovery in milder cases. In patients with more severe symptoms not responding to supportive measures, dantrolene (1–10 mg/kg/day in divided doses), bromocriptine (2.5–15 mg tid), or amantadine (200–400 mg/day) have been reported to reduce time to recovery and decrease mortality. ECT may be effective if symptoms are refractory to supportive care and pharmacotherapy, even late in the course of NMS, and in patients with severe rigidity and catatonia (Strawn et al 2007)

#### 8.8.1.2.1 Guidelines for Treatment (Strawn et al. 2007)

Mild or early NMS: Discontinue antipsychotics, use supportive measures and benzodiazepines

Moderate NMS (rigidity and temperatures 38–40 °C, HR 100–120 bpm): Discontinue antipsychotics, use supportive measures, and use benzodiazepines or amantadine or bromocriptine.

Severe NMS: (severe rigidity, catatonia, temp >40, HR > 120 bpm) Discontinue antipsychotics, use supportive measures and use dantrolene or bromocriptine or amantadine. Consider ECT.

#### 8.8.1.2.2 Guidelines for Rechallenge

There is a 30 % risk of recurrence following subsequent rechallenge with antipsychotics (Pope et al. 1991). At least 2 weeks after recovery from NMS should be allowed before rechallenge with antipsychotics. Reduce potential risk factors and consider alternate medications. Low doses of low potency typical antipsychotics or atypical

antipsychotics should be titrated gradually after a test dose. Patients should be carefully monitored for early signs of NMS. Ideally, rechallenge should occur in a hospital.

### 8.8.2 Serotonin Syndrome (SS)

Serotonin syndrome is a potentially life threatening adverse reaction resulting from therapeutic drug use, intentional or accidental overdose of drug or from interactions between drugs that result in excess of serotonergic agonism of the central and peripheral serotonergic receptors. The serotonin syndrome can range from mild to moderate to lethal. Differentiating serotonin syndrome from neuroleptic malignant syndrome can be difficult in a patient receiving both serotonergic and antipsychotic medications.

Overstimulation of serotonin receptors can be caused by precursors of serotonin or by serotonin agonists like buspirone, L-dopa, lithium, LSD, L-tryptophan, and trazodone, from decreased serotonin metabolism from MAOIs, from increased serotonin release from amphetamines, cocaine, MDMA ("ecstasy"), fenfluramine, or from inhibition of serotonin reuptake from antidepressants, meperidine, and tramadol.

#### 8.8.2.1 Clinical Features

The symptoms and signs of serotonin syndrome include (Boyer and Shannon 2005):

1. Neuromuscular symptoms: Delirium, agitation, anxiety, irritability, affective instability, restlessness, ataxia/incoordination, muscle rigidity, myoclonus, tremor, hypereflexia, clonus, trismus, teeth chattering, seizures.
2. Gastrointestinal symptoms: Nausea, vomiting, diarrhea, incontinence.
3. Autonomic symptoms: Hypertension, hypotension, tachycardia, diaphoresis, shivering, sialorrhea, mydriasis, tachypnea.
4. Hyperthermia.

Differential diagnosis for serotonin syndrome includes infections, toxic-metabolic delirium, alcohol withdrawal delirium, extrapyramidal side-effects, adrenergic or anticholinergic toxicity, neuroleptic malignant syndrome, malignant hyperthermia, pheochromocytoma, and carcinoid tumor.

*Clinical course and outcome*: Symptom onset is rapid, usually developing within 6 h of an increase or addition of a serotonergic agent and typically resolves within 24 h (Iqbal et al. 2012). Patients with mild SS may present with chronic or subacute symptoms. Serotonin syndrome is usually self-limited, with an uneventful resolution, once the offending agent has been discontinued.

Nonspecific laboratory findings may include elevated total white blood cell count, CPK levels, transaminases, and decreased serum bicarbonate level. Severe cases can result in complications like disseminated intravascular coagulation, rhabdomyolysis, metabolic acidosis, renal failure, myoglobinuria, and adult respiratory distress syndrome.

#### 8.8.2.2 Management of SS

Discontinuation of serotonergic agents, supportive measures including intravenous fluids, cooling blankets, treating autonomic dysfunction usually reverses the symptoms in mild cases. Benzodiazepines can be used to treat tremors and agitation. In more severe cases, serotonin antagonists—cyproheptadine and chlorpromazine, have shown to reverse the symptoms (Gillman 1999; Graudins et al. 1998). Cyproheptadine, 4–8 mg orally or through the nasogastric tube, repeated every 6 h up to a maximum of 32 mg/day has produced rapid resolution of symptoms. Antipsychotic agents with 5-HT2A antagonist activity such as chlorpromazine may reverse the symptoms in severe cases of SS. Chlorpromazine should not be routinely used to manage SS, especially if the patient is hypotensive and/or NMS cannot be excluded (Iqbal et al 2012).

*Drug rechallenge*: Switch to non-serotonergic antidepressant if possible. Consider 6 weeks serotonin drug free period before restarting a serotonergic agent.

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