Introduction

Evidence-based guidelines for the perioperative management of psychotropic drugs are lacking. The level of evidence is low and is based on case reports, open trials, and non-systematic reviews. One of the most important factors influencing perioperative morbidity and mortality is related to anaesthesia itself, and the increase in this risk due to the combination of anaesthetic drugs with other drugs, such as psychotropics ***(Huyse, 2006).***

However, challenges for the anaesthetist may arise from the nature of the psychiatric condition itself, interactions of psychoactive and anaesthetic drugs, and the problems caused by the condition requiring surgery (e.g. electrolyte derangement and prolonged periods of fasting). The management of patients on psychoactive medications in the perioperative period is largely based on the individual clinician's experience ***(Becker, 2008).***

Classically, psychiatric illnesses were thought to be due to biochemical imbalances within the central nervous system (CNS).

This belief was based on the pharmacological actions of drugs known to be efficacious in the treatment of such illness. We now know that this is, at best, an overly simplistic view and that many of

the psychoactive drugs affect several neurochemical pathways.

Psychoactive drugs can be classified as *antidepressants, mood stabilizers, antipsychotics and anxiolytics* ***(Peck et al., 2010).***

The anaesthetist has to incorporate these agents in premedication and should anticipate their interactons with anaesthetic technique. Modern anaesthesia is flexible. This flexibility offers an apportunity to reduce or avoid drug-drug interactions. Before the decision on type of anaesthesia, direct and indirect effects through drug-drug interaction should be considered. Therefore, we recommend a critical evaluatin of use and duration, as well as monitoring of psychoactive drug prescriptions at pre-assessment; we need to determine the possible interactions with drugs for coexisting physical morbidity.as well as drug-drug interactions with the proposed anaesthetics, effects such as hemodynamic instability. Including cardiac conduction changes, and the effects on CNS functioning in case of postoperative metabolic instability. A severity grading for drug-drug interactions pertinent to the anaesthesiologist was presented ***(Hamerman, 1999).***

Aim of the Work

- To clarify the guidelines for psychotropic drug management in the perioperative period with focus on risk management to prevent perioperative mortality, physical morbidity, withdrawal problems and acute or long term relapse of psychiatric morbidity, thereby avoiding last minute cancellation of surgery.

- To summarize the commonly used groups of psychoactive medications and their interactions with anaesthetic drugs. Thus helping in prevention of intraoperative complications resulting from those interactions. Also prevention of postoperative emergence of psychosis and agitation.

Classifications of psychoactive drugs

Psychoactive drugs are licensed drugs taken to exert an effect on the chemical makeup of the brain and nervous system. Thus, these drugs are used to treat mental disorders. Usually prescribed in psychiatric settings, these drugs are typically made of synthetic chemical compounds, although some are naturally occurring, or at least naturally derived. Since the mid-20th century, such medications have been leading treatments for a broad range of mental disorders and have decreased the need for long-term hospitalization therefore lowering the cost of mental health care ***(Brink, 2008).***

- There are six main groups of psychiatric medications.

- Antidepressants, which treat disparate disorders such as clinical depression, dysthymia, anxiety, eating disorders and borderline personality disorder.

- Stimulants, which treat disorders such as attention deficit hyperactivity disorder and narcolepsy, and to suppress the appetite.

- Antipsychotics, which treat psychoses such as schizophrenia and mania.

- Mood stabilizers, which treat bipolar disorder and schizoaffective disorder.
- Anxiolytics, which treat anxiety disorders.
- Depressants, which are used as hypnotics, sedatives, and anesthetics ***(Schatzberg, 2000).***

- Hallucinogens have been used in psychiatric medication in the past, and are currently being reevaluated for several uses.

Also, in the last two decades, antiepileptic drugs (AEDs) have been used for the management of psychiatric disorders. Their greatest use has been in the management of bipolar disorders, ***(Sussman and Ettinger, 2007)*** as well as pain disorders ***(Eisenberg et al., 2007).*** Although more recent studies have demonstrated the efficacy of AEDs in anxiety disorders, unipolar depression, and the process of detoxifying patients from alcohol and cocaine. The AEDs with established psychotropic effects (for example, carbamazepine, valproate, and lamotrigine) have been found to cause an increase in 5 hydroxytryptamine (5HT). Thus may explain their effect ***(Andres et al., 2001).*** These main groups of psychoactive drugs are further categorized into many categories according to their chemical structures or mechanism of action on certain

neuorotransmitters. Also there is marked overlap among the indications of these drugs ***(Schatzberg, 2000).***

1- Antidepressants:

The introduction of reserpine as an antihypertensive in the 1950s and the subsequent finding of its ability to induce depression by inhibiting the storage of amine neurotransmitters in presynaptic nerve endings led to the amine hypothesis of depression. This discovery led to the development of medications with activity on neurotransmitters at the synaptic cleft ***(Katzung, 2003).***

Despite the large number of antidepressants that have been introduced into the market since the 1950s, the vast majority of antidepressants are classified as having their primary actions on the metabolism, reuptake, or selective receptor antagonism of serotonin, norepinephrine, or both. Whereas these agents' immediate actions with one or more monoamine neurotransmitter receptors or enzymes have led to the current classification of antidepressants, (selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), mixed action agents, selective norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), and alternative -non-traditional- antidepressants).

Readers should keep in mind that there is no classification scheme that accurately reflects the actions of all the drug classes ***(Ciraulo and Shader, 2011).***

1.1- SSRIs—selective serotonin reuptake inhibitors:

This group of drugs, including fluoxetine (Prozac)*, paroxetine (Paxil), fluvoxamine (Luvox), citalopram (celexa), escitalopram (cipralex) and sertraline (Zoloft), is usually the first choice for treatment of depression and anxiety problems. These medications are known to have milder side-effects than some other antidepressants.

1.2- SNRIs-serotonin and norepinephrine reuptake inhibitors:

This class of medications includes venlafaxine (Effexor), duloxetine (cymbalta) and desvenlafaxine (Pristiq). These drugs are used to treat depression, anxiety problems and chronic pain.

1.3- NDRIs- norepinephrine and dopamine reuptake inhibitors:

The medication available in this class is bupropion (Wellbutrin, Zyban). When used to treat depression, it is often given for its energizing effects, in combination with other antidepressants. It is also used to treat attention-deficit/hyperactivity disorder and as a smoking cessation aid.

1.4- TCA- cyclics or tricyclic antidepressants:

This older group includes amitriptyline (Elavil), maprotiline (Ludiomil), imipramine (Tofranil), desipramine (Norpramin), nortriptyline (Novo- Nortriptyline) and clomipramine (Anafranil).

Because these drugs tend to have more side-effects than the newer drugs, they are not often a first choice for treatment. however, when other drugs do not provide relief from severe depression, these drugs may help ***(Ciraulo and Shader, 2011).***

1.5- MAOIs-monoamine oxidase inhibitors:

Monoamine oxidase inhibitors, or MAOIs, such as phenelzine (Nardil) and tranylcypromine (Parnate) were the first class of antidepressants. MAOIs are effective, but they are not often used because people who take them must follow a special diet. A newer MAOI, moclobemide (manerix), can be used without dietary restrictions; however, it may not be as effective as other MAOIs.

1.6- NaSSAs-noradrenergic and specific serotonergic antidepressants:

Mirtazapine (Remeron), the medication available in this class, is the most sedating antidepressant, making it a good

choice for people who have insomnia or who are very anxious. This medication also helps to stimulate appetite. common side-effects are drowsiness and weight gain.

Common antidepressant drugs in the market include:

- Fluoxetine (Prozac), SSRI
- Paroxetine (Paxil, Seroxat), SSRI
- Citalopram (Celexa), SSRI
- Escitalopram (Lexapro), SSRI
- Sertraline (Zoloft,lustral,moodapex), SSRI
- Duloxetine (Cymbalta), SNRI
- Venlafaxine (Effexor), SNRI
- Bupropion (Wellbutrin), NDRI.
- Mirtazapine (Remeron), NaSSA
- Isocarboxazid (Marplan), MAOI
- Phenelzine (Nardil), MAOI
- Imipramine (tofranil) TCA
- Amitriptyline (Elavil) TCA

(Stephen et al., 2004)

A number of antidepressants were introduced after SSRIs. *Venlafaxine* is a nonselective serotonin and norepinephrine reuptake inhibitor. *Desvenlafaxine*, the primary metabolite of venlafaxine, has a similar profile to its parent

compound, but dosing may be easier. *Duloxetine* is also a nonselective serotonin and norepinephrine reuptake inhibitor, but has greater potency than venlafaxine ***(Detke et al., 2002).***

Bupropion is an aminoketone that in vivo may block norepinephrine reuptake via its active metabolite hydroxylbupropion and also increase dopamine activity by an unknown mechanism. These newer antidepressant offer some advantages in tolerability over the older agents and perhaps more importantly have different mechanisms of action, which may provide alternatives for patients who do not respond to other antidepressants ***(Ciraulo and Shader, 2011).***

2-Anxiolytics:

Anxiolytics are another frequently prescribed class of medications used in a broad spectrum of patients. The evolution of anxiolytics has seen a progression to agents with more specific pharmacodynamic actions in an attempt to produce a more targeted effect with a narrower side-effect profile ***(Nutt, 2005).***

2.1-Sedatives:

The classic definition of a sedative agent involves a substance that can reduce anxiety and produce a calming

anxiety and produce a calming effect with hopefully little effect on motor skills or mental function. This blending of efficacy and toxicity in the previous definition resulted from the activity of classic anxiolytics (i.e., barbiturates and to a lesser extent benzodiazepines).

Benzodiazepines produce their effects by acting as a positive allosteric modulator of the GABA type A receptor. variety of potential side effects (e.g., drowsiness, impaired judgment, diminished motor skills, lethargy) may occur ***(Outhoff, 2010).***

Thus, although benzodiazepines are effective anxiolytics (and hypnotics), the side-effect profile and abuse potential of these agents seriously limit the utility of benzodiazepines ***(Stahl and Muntner, 2000).***

Despite the common use of benzodiazepines, there remains a great need for safe and effective Anxiolytics.

Buspirone, a 5HT1A partial agonist, was created to be an anxiolytic without the drawbacks of benzodiazepines. The mechanistic differences associated with buspirone has led to a somewhat effective anxiolytic that has a delayed onset of action (more analogous to that of antidepressants).

The lack of hypnotic, anticonvulsant, or muscle relaxant properties; and a reduced potential for abuse and sexual side effects has made it a favourite option as an anxiolytic ***(Ciraulo and Shader, 2011).***

2.2-SSRIs and SNRIs

SSRIs or serotonin–norepinephrine reuptake inhibitors (SNRIs) are the most commonly prescribed psychotropics for the treatment of GAD, also Buspirone and
Other new antidepressant agents *eg.Mirtazepin* are commonly used nowadays ***(Ciraulo and Shader, 2011).***

2.3-Beta-adrenergic blockers: such as propranolol (Indral), have been used in the past to treat anxiety disorders. However, the effect is temporary and may facilitate the emergence of depression. Unfavourable list of side effects including hypotension, hypoglycemia and impotence Therefore, they should be avoided ***(Keller et al., 1999).***

3-Mood stabilizers:

Mood stabilizers are groups of drugs used for treatment of certain mood disorders including bipolar disorder (manic depressive disorder), Dysthymic disorder and cyclothymic

disorder, which are atypical forms of bipolar disorder. Mood stabilizers are a critical component in the treatment of patients with bipolar disorder. Lithium carbonate, (AEDs) eg, carbamazepine, lamotrigine, and the second-generation (atypical) antipsychotics are effective in the acute episode, as well as in the prevention of future episodes of depression and mania. Only 50–60% of patients have an adequate response to one of the mood stabilizers Alone, the use of multiple medications is often necessary ***(American Psychiatric Association, 2002).***

Lithium:

The primary clinical indications for lithium in psychiatry are the treatment of acute manic and hypomanic episodes, maintenance treatment of patients with recurrent bipolar I and II and unipolar affective disorders, and as an augmenting agent for acute refractory MDD ***(Hirschfeld et al., 2002).***

AEDs:

While a large number of antiepileptic drugs (AEDs) have become available for the treatment of epilepsy, many of these agents are now utilized for conditions other than epilepsy. Two main categories of non epileptic use are psychiatric disorders and chronic pain ***(Goodnick, 2006).*** The use of AEDs in

psychiatric disorders is based on the belief that there are shared biological mechanisms involved in epilepsy and these disorders eg., Lamotrigine has antidepressant properties. Carbamazepine, valproate, lamotrigine and oxcarbazepine appear to have mood stabilizing properties while gabapentin, pregabalin, and tiagabine have anxiolytic benefits ***(Toczek et al., 2003).***

4- Antipsychotics:

Antipsychotic medications can reduce or relieve symptoms of psychosis, such as delusions (false beliefs) and hallucinations (seeing or hearing something that is not there). Formerly known as major tranquilizers and neuroleptics, antipsychotic medications are the main class of drugs used to treat people with schizophrenia. They are also used to treat people with psychosis that occurs in bipolar disorder, depression and Alzheimer's disease. Other uses of antipsychotics include stabilizing moods in bipolar disorder, reducing anxiety in anxiety disorders as people with anxiety and mood disorders may benefit from taking antipsychotics in addition to antidepressants or mood stabilizers. When used in this way, antipsychotics may help to control symptoms such as irritable or depressed mood, disorganized thinking and troubles in concentrating and remembering (***Miyamoto et al., 2005)***

Antipsychotic medications are generally divided into two categories, first generation (typical) and second generation (atypical). The main difference between the two types of antipsychotics is that the first generation drugs block dopamine and the second generation drugs block dopamine and also affect serotonin levels. Evidence suggests that some of the second generation drugs have milder movement related side-effects than the first generation drugs ***(Miyamoto et al., 2005).***

First generation (typical) antipsychotics:

These older medications include chlorpromazine(once marketed as Largactil), flupenthixol (Fluanxol), fluphenazine (modecate), haloperidol (haldol), loxapine (Loxapac), perphenazine (Trilafon), pimozide (Orap), trifluoperazine (Stelazine), thiothixene (Navane) and zuclopenthixol (clopixol) ***(Stephen and Stahl, 2002).***

Second generation (atypical) antipsychotics:

Medications available in this class include risperidone (Risperdal)*, quetiapine (Seroquel), olanzapine(Zyprexa), ziprasidone (Zeldox), paliperidone (Invega), aripiprazole (Abilify) and clozapine (clozaril). clozapine is exceptional in that it often works even when other medications have failed; however, because it requires monitoring of white blood cell