

# Psychiatric Drugs in Medical Practice

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## 1. Introduction

Psychiatric symptoms are very frequent in medical practice, up to 40% of the people that have physical problems present anxiety or depressive symptoms associated to physical illness. Due to this, psychiatric liaison is an important part of hospital attention and many people usually have psychiatric drugs associated to other treatments.

Psychiatric drugs usually are classified into six great families depending on their principal focus of action or their use in the main psychiatric disorders:

- Antidepressants: these drugs act on depressive illness through the action on various neurotransmitter systems: serotonin, noradrenaline and dopamine. The most used of these are SSRI (serotonin selective reuptake inhibitors), because of their efficacy and good profile of side effects.
- Antipsychotics: they are used in the control of psychotic symptoms and as major tranquilizers. Antipsychotics are classified on first generation and second generation. The first of them act upon dopamine receptors and the second ones upon serotonin and dopamine receptors to have antipsychotic effects. This second generation substances have less side effects and a different profile of action.
- Anxiolytics: the most widely used are benzodiazepines, which act upon a specific GABA receptor. This family of drugs has a very quick effect, but they aren't recommended for a long time use because they can produce dependence and their effects are limited. They are also used like anticonvulsivants.
- Antiepileptics: This group of drugs is used in psychiatry for the maintenance and control of bipolar disorders, and they are useful too like antiaggressive drugs. The therapeutic drug monitoring is necessary when some of these substances are administrated because of their potential toxicity and the pharmacological interactions with other treatments.
- Lithium: it is a salt used for control of manic symptoms and maintenance of bipolar disorders. Its action mechanism is unknown, despite its usefulness and generalized utilization. It's necessary to control its plasmatic level into a tight range to avoid toxicity and to achieve its function.
- Other drugs widely used in psychiatric disorders: methadone, anticholinesterases, stimulants, alcohol aversives are also important due to their side effects and their pharmacologic interactions.

## 2. Antidepressants

First antidepressant drugs were a casual finding and they affect to various neurotransmitters systems. Usually these old drugs produce many secondary effects. Afterwards, some hypotheses have emerged about the neurotransmission implicated in depression (monoamines: serotonin, noradrenalin and dopamine). Drug development progresses in parallel to this investigation so more selective drugs appeared as Selective Serotonin Reuptake Inhibitors, (from now on SSRIs), ameliorating secondary effects.

Antidepressant classification depends on the assumption of their action mechanism. Following that schema, there are eight different pharmacological mechanisms at least. The most of the antidepressants block monoamine reuptake, but others block alpha-2 receptors or monoamineoxidase enzyme.

### 2.1 Monoamine reuptake inhibitors

#### 2.1.1 Tricyclic and tetracyclic antidepressants (TCA)

The tricyclic and tetracyclic branch of antidepressants has a demonstrated and high efficacy, only limited by their sedative and anticholinergic effects. They act on a huge number of receptors, and are cardiotoxic in case of overdoses, as anticholinergic toxicity and convulsions.

**Pharmacological actions:** A significant part is absorbed totally after oral administration. They have a significant metabolism by first-pass. Maximum plasmatic concentration is reached in 2-48 hours but equilibrium appears after 5-7 days. Their long half-life allows them to be used once in a day. Clearance of tricyclics is dependent primarily on hepatic cytochrome P450 (CYP) oxidative enzymes.

**Effects on organs and special systems:** Significant effects on the cardiovascular system appear at therapeutic dose: they are classified as anti-arrhythmic type IA, since they interrupt the ventricular fibrillation and can increase the collateral blood flow of ischemic heart. In overdose they are highly cardiotoxic and cause a decrease in contractility, increased irritability myocardial, hypotension and tachycardia.

#### 2.1.2 Main therapeutic indications

**Depression:** treatment of one major depressive episode and prophylaxis of one major depressive episode (main directions); depression in Bipolar type I disorder (in resistant cases, with many precautions to prevent swinging: associated with anticonvulsivants or lithium); one depressive episode with psychotic manifestations almost always requires the simultaneous administration of an antipsychotic drug and an antidepressant; Disorder mood due to a general medical disease with depressive features

- Panic disorder.
- Generalized anxiety disorder.
- Obsessive-compulsive disorder: clomipramin especially. None of the others seems so effective.
- Others: Alimentary conduct disorder and pain disorder.

### 2.1.3 Precautions and adverse reactions

- Psychopathological effects: possibility of inducing a manic episode, especially in patients with a history of Bipolar disorder. It has been also described that the tricyclic antidepressants can exacerbate or precipitate psychotic symptoms in vulnerable patients.
- Anticholinergic effects: They consist of dry mouth, constipation, blurred vision, urinary retention, closed angle glaucoma
- Sedation.
- Effects on the autonomous nervous system: orthostatic hypotension, profuse sweating, palpitations, and increased blood pressure.
- Effects on the cardiovascular system: tachycardia, QT prolongation, flattening of T wave, ST depression, etc.
- Neurological effects: Delirium (cholinergic effects). Psychomotor stimulation. Parkinsonism, dyskinesia, akathisia, and inclusive by dopaminergic blockade: neuroleptic malignant syndrome. Finally there is a relatively small risk of induce convulsions, so in risky patients is encouraged to use lower doses.
- Allergic and haematological effects: rash, and much less frequently jaundice, agranulocytosis, leukocytosis, leukopenia, and eosinophilia.
- Other: frequent weight gain, sexual dysfunction, digestive discomfort (nausea, vomiting) and much more rarely syndrome of inappropriate secretion of antidiuretic hormone.
- Avoid in pregnancy and lactation. Use with caution in patients with kidney or liver disease. Increased risk of cardiac adverse effects if it is associated to electroconvulsive therapy. If there is a history of heart disease the TCA administration must start with low-dose, gradually increasing while maintaining a surveillance of cardiac functions. Their administration must be suspended the prior days to a surgical intervention, due to the risk of hypertensive episodes. Prior to starting treatment with any TCA basal EKG should be made. Try to avoid in patients with closed glaucoma, if necessary you may need to manage at the same time pilocarpine eye drops.

### 2.2 Serotonin Selective Reuptake Inhibitors (SSRIS)

Serotonin is a neurotransmitter especially relevant in neurobiological basis in affective disorders, compulsive-obsessive disorder, and aggressive behavior.

SSRIs block the serotonin reuptake pumps action, augmenting serotonin concentration in synapsis and postsynapsis receptors' occupation. Though this effect appears early during treatment, clinical effects delay 3-6 weeks.

They are metabolized at liver, present a low affinity except for serotonin receptors, are enough sure in overdoses, change sleep structure (reduce latency and total amount of REM sleep) and might be avoid used with MAOIs, due to the risk of serotonergic syndrome.

**Therapeutic indications:** Depression; Anxiety disorders, including Obsessive-Compulsive Disorder; Bulimia nervosa; Psychosomatic disorders

**Precautions and adverse reactions:** Sexual dysfunction, digestive discomfort, weight gain, headache, serotonergic syndrome, anticholinergic effects, and other: hematological effects,

alterations in electrolytes and glucose, allergic and endocrine reactions, galactorrhea, and abrupt suspension discontinuation syndrome.

### 2.3 Noradrenalin selective reuptake inhibitors (reboxetine)

It selectively inhibits the reuptake of norepinephrine, but it has little effect on the reuptake of serotonin or dopamine. It is structurally related to fluoxetine. It has little affinity for muscarinic receptors or cholinergic and does not interact with the  $\alpha_1$ ,  $\alpha_2$ , adrenergic beta, serotonergic, dopaminergic or histaminergic receptors. Therefore, SSRIs and reboxetine have some complementarity effects and are used together in the clinic in some resistant depressions.

Reboxetine has a rapid absorption; food does not affect the speed of it. It is metabolized in liver, mainly through the 3A4 isozyme of cytochrome P450 and it is excreted by kidney.

**Medical indications:** depressive disorders and social phobia. Adverse reactions: the most common are: faltering urination, headache, constipation, nasal congestion, sweating, dizziness, dry mouth, decreased libido, insomnia. Hypertension and tachycardia can appear at high doses, as well as psychomotor retardation if it is taken with alcohol. The syndrome of inappropriate secretion of antidiuretic hormone is exceptional. Precautions: contraindicated in pregnancy and breastfeeding. The doses must be reduced in elderly patients and serious renal impairment.

### 2.4 Inhibitors of the reuptake of serotonin and norepinephrine

#### 2.4.1 Venlafaxine

It is a potent inhibitor of the reuptake of serotonin, at higher doses inhibits the reuptake of noradrenaline and slightly inhibits the reuptake of dopamine.

The absorption is good at digestive level and suffer important hepatic metabolism, by CYP 2D6 isoenzyme, so some SSRIs isozyme inhibitor drugs may increase plasma levels of venlafaxine, giving effects at low doses which are resolved once the inhibitor drug is withdrawn.

**Therapeutic indications:** depression, generalized anxiety disorder. Venlafaxine can be effective in: OCD, panic disorder, agoraphobia, social phobia, Attention Deficit and Hiperactivity Disorder (ADHD) and treatment of chronic pain. The most frequent side effects are nausea (less frequent with the retard formulation), drowsiness, dry mouth, dizziness, anxiety, constipation, asthenia, sweating, anxiety, anorexia, blurred vision, sexual dysfunction. A syndrome of discontinuation can appear if it stopped suddenly (nausea, drowsiness and insomnia...), so it should be reduced gradually. At high doses can precipitate high blood pressure.

It should be used cautiously in patients with pre-existing hypertension, administering lower doses, avoid its use in pregnancy and lactation and in children has not established safety or efficacy. In major liver or kidney function deterioration doses must be reduced. Venlafaxine overdosage may be more serious than with SSRIs and similar to tricyclic. It may be appropriate to avoid prescribing venlafaxine to patients who have high risk of poisoning.

#### 2.4.2 Duloxetine

Like venlafaxine, it inhibits the reuptake of both serotonin and norepinephrine, Duloxetine has a minimal affinity for dopamine and histamine receptors.

It has significant hepatic metabolism, with many metabolites. It's a moderate inhibitor of CYP 2D6. Its excretion is renal.

**Clinical indications:** depression, Treatment of diabetic peripheral neuropathic pain. **Contraindications:** it must never be administered in patients with liver failure and it's not recommended in patients with terminal stage renal disease. Secondary gastrointestinal effects are common: nausea, dry mouth and constipation. Diarrhea and vomiting are less frequent. Insomnia, dizziness, somnolence and sweating are also common. Sexual dysfunction appears less frequently than with SSRIs, particularly in women.

### 2.4.3 Inhibitors of the reuptake of norepinephrine and dopamine (bupropion)

It is usually more effective on symptoms of depression than anxiety and quite useful in combination with SSRIs. It has some dopaminergic effects and therefore can induce mild psychostimulant effects. The mechanism of action is not known with accuracy. It seems that weakly inhibits the reuptake of dopamine, raising levels of it in the nucleus accumbens. This increase in dopamine levels in the "area of reward" of the brain may be responsible for the use of bupropion in the cessation. Some data indicate that it exerts its antidepressant effects increasing the functional efficiency of the noradrenergic systems. Apparently it has no effect on the serotonin system, so it is not effective to block panic attacks.

**Pharmacokinetics:** Good absorption at digestive tract; extensively metabolized in the liver. It seems to inhibit the isozyme CYP 2D6. It is also important to note that drugs that inhibit the isozyme will increase levels of bupropion, raising the risk of seizures.

**Indications:** depression: because of its stimulating effect, is used in depressive patients with fatigue and lack of concentration. The improvement of the sleep at the beginning of the treatment is less common than with other antidepressants, but does not alter sleep architecture. It is useful for abandonment of tobacco, in combination with conduct programs. It has also proposed its use in disorders attention deficit and on substance abuse (seems to decrease the craving in cocaine addiction).

**Contraindications:** Bulimia and anorexia, history of seizures or epilepsy, alcohol consumption, recent discontinuation of benzodiazepines, organic brain disease, cranial traumatism or EEG discharges. It isn't recommended in pregnancy or lactation.

The most common side effects are high respiratory discomfort, nausea, headache and insomnia. There may also be anxiety, agitation and irritability. It's the antidepressant with less inhibition of sexual function and it is more likely to reduce the weight than to increase it. The retard formulation is associated with an incidence of seizures of 0.1% at usual doses. Exceptionally it could cause psychotic hallucinations, delusions, catatonia symptoms, as well as delirium (by enhancing dopamine). It can increase blood pressure in previously hypertensive patients. There is no indication of significant effects on the heart, kidney or liver function.

### 2.5 Blockers of presynaptic autorreceptors: Mirtazapine

Its unique mechanism of action is blocking the receptors Alpha<sub>2</sub> pre and post synaptic, as well as the serotonergic 5HT<sub>2</sub> and 5HT<sub>3</sub> receptors. In contrast to the TCA, mirtazapine has

low affinity receptors  $\alpha_1$  blocking. It has little interaction with receptors for acetylcholine, but blocks histamine receptors in a powerful way.

It is proposed that the antagonism of the presynaptic  $\alpha_2$  receptors leads to a significant increase in noradrenergic neurotransmission. This augmentation produced by mirtazapine increases the release of serotonin, producing the antidepressant effect.

Pharmacokinetics: rapid and complete absorption in the digestive tract; plasma clearance: up to 30% slower if there is impaired liver function, up to 50% slower if there is deterioration of kidney function. It has hepatic metabolism, by CYP 1A2, 3A4, 2D6 and CYP2C9.

Side effects: drowsiness (50% of treated patients). Managing at bedtime can be reduced. It appears more at low doses. It causes weight gain, increase in appetite, dry mouth, dizziness and lower risk of sexual dysfunction than with other antidepressants.

Precautions: it can increase levels of cholesterol and triglycerides, increase transaminases, reduce of the absolute count of neutrophils to 500/mm<sup>3</sup> or below (some of the patients had symptomatic infections), it is a reversible alteration and is more likely to occur if there are other risk factors for neutropenia. In elderly individuals, kidney or liver failure can be necessary to use lower doses.

## 2.6 Serotonergic modulators: Trazodone

Its mechanism of action is the modulation of serotonergic neurotransmission; it is a relatively specific inhibitor of the reuptake of serotonin. It does not cause any anticholinergic effects. It has  $\alpha_1$  adrenergic antagonism and antihistaminergic activity, so has more sedative effects than other antidepressants. The sedative effects appear to one hour after administration and antidepressant effects at 2-4 weeks.

Indications: Depression (especially effective in regulating the quality of sleep). Also it has been proposed for use in anxiety disorder, disorder panic, obsessive-compulsive disorder, insomnia, severe agitation in older people (50 mg/day), post-traumatic stress disorder (PTSD) and as coadjuvant in schizophrenia

Most common side effects: sedation (it is often used at low doses: 50 - 100 mg/day to induce sleep or treat insomnia due to SSRI); nausea, postural hypotension, priapism (rare, but dangerous).

Special situations: it has been rarely associated with cardiac arrhythmias and it should be used cautiously in patients with cardiac disease. It is contraindicated in pregnancy and lactation. It should be used cautiously in patients with kidney or liver disease.

## 2.7 Monoamine Oxidase Inhibitors (MAOIs)

They inhibit the enzyme MAO, who is responsible for the oxidative deamination of neurotransmitters such as serotonin, norepinephrine, or dopamine.

There are two ways for MAO enzyme: MAOa and MAOb. The MAOa metabolizes the monoaminergic neurotransmitters more closely associated with depression (norepinephrine and serotonin). The MAOb acts upon some aminergic substrates, called protoxins, toxins

that can cause neural damage. Therefore the inhibition of the MAOa is associated both hypertensive effects and therapeutic effects. Inhibition of the MAOb is associated with the prevention of neurodegenerative disorders, such as Parkinson's disease processes.

The MAO is widely distributed in the body. The blockade of the MAOa in the gastrointestinal tract is responsible for the "cheese effect". It consists of a severe hypertensive crisis that occurs in patients who are taking MAOIs and ingest food containing tyramine. Tyramine is usually metabolized in the digestive tract but the blocking of the MAOa allowed their passage into general circulation. So, patients in treatment with IMAOs must follow a tyramine-restricted diet.

They exert their effects primarily in the CNS. They act on the mood, decreased sleep and insomnia and daytime sleepiness. They are characterized by a significant reduction of REM sleep. The MAOIs are not considered antidepressants in frontline due to restrictions in the diet, its pharmacological interactions and its broad side effect profile.

**Medical indications:** depression, Panic disorder, PTSD, eating disorders, social phobia and pain disorder.

**Side effects:** the most frequent: orthostatic hypotension, insomnia, weight gain, dry mouth, headache, edema, and sexual dysfunction. Rare: spontaneous hypertensive crisis. Rarely: paresthesias, myoclonus, and muscle ache. Confusion or drunkenness (it is necessary to reduce doses). They have few liver toxic effects and less cardiac effects than the tricyclic antidepressants.

RIMA (reversible monoamine oxidase inhibitor: moclobemide) can produce dizziness, nausea and insomnia. It has less gastrointestinal effects than SSRIs and no sexual effect.

**Special situations:** caution in patients with renal, cardiovascular disease or hyperthyroidism. In diabetes they can reduce blood glucose, so physician can be forced to change the dose of hypoglycaemic drugs. They have been associated to manic induction in individuals in depressive phase of a Bipolar disorder type I and psychotic decompensation in patients with schizophrenia. They are contraindicated in pregnancy and lactation. In elderly: the MAO activity increases with age, so the dose of MAOIs to elderly people and young adults are the same. Phenelzine and isocarboxazid have been associated with significant risk of hepatotoxicity.

**Drug interactions:** can be serious and even fatal. They can never be administered with drugs that increase the concentrations at the synaptic level of biogenic amines: most antidepressants. There is risk of trigger a serotonin syndrome. They enhance alcohol and barbiturates, and other CNS depressants sedative effects. It is important to make a washing period when changing treatment.

Rich in tyramine foods must be avoided during treatment with a MAOIs: cheeses, cured meats, sausages, bananas, avocados, dried figs, smoked fish, chocolate, alcoholic beverages.

### 3. Classic and second generation antipsychotics

#### 3.1 Classic antipsychotics

Among classic antipsychotics (AP) there is no one that has a clear superiority over the others, so choice must be made depending on previous response or side effects profile.

The AP are well absorbed orally, although their bioavailability is altered with the intake of certain foods, coffee, calcium antacids and excessive consumption of nicotine, which can reduce the absorption from the intestinal tract. They have great solubility and easily cross the blood-brain barrier.

Classic antipsychotics include: Chlorpromazine, levomepromazine, flufenazine, perfenazine, trifluoperazine, haloperidol, zuclopentixol, molindone, and pimocide.

The AP show a great affinity for plasma proteins (85-90%), which involves risk of toxicity when other drugs that also bind to proteins are running simultaneously. On the other hand, given that they pass easily through the blood-brain barrier, concentrations achieved in CNS doubles those that are quantified in the peripheral circulation. They also cross the placental barrier, reaching to the fetus during pregnancy. Due to their lipophilic properties, antipsychotics are stored in the peripheral fat, so dialysis is ineffective in cases of overdose.

Traditional antipsychotic drugs are metabolized in the liver via hydroxylation and demethylation in cytochrome P450 processes. Some, such as haloperidol, suffer an additional glucuronidation and remain active as dopamine antagonists. Major isozymes in the metabolism of these drugs are the 2D6 and the 3A4. It is estimated that between 5 and 10% of individuals in white, and one much higher proportion of black individuals are slow track metabolizers of cytochrome P450 2D6, so it is predictable that submit side effects with a greater frequency and severity.

The AP are removed primarily by urine and feces, through bile, but also by the saliva, tears, sweat, and breast milk. The elimination half-life varies between 18 and 40 hours. In the elderly, who often have impaired kidney function to a greater or lesser extent, physician should proportionally reduce the dose.

### 3.1.1 Clinical Indications

The AP have been the most commonly used drugs in the treatment of acute episodes and as therapy for schizophrenia maintenance. Its mechanism of action is basically attributed to the blockade of receptors D2 between five types of recipient described dopamine. The blocking dopamine at mesolimbic track is responsible for the therapeutic effect, with reduction of delusions and hallucinations. For its part, the nigrostriada via controls movement, and so its blockade produces akathisia and dystonia and parkinsonism. The dopaminergic mesocortical via seems involved in the mediation of negative and cognitive symptoms of schizophrenia, and last but not least, the tubero-infundibular that controls the secretion of prolactin, blocked by antipsychotic medication stimulates production with galactorrhea.

The usefulness of antipsychotics in the treatment of affective disorders that have psychotic symptoms, as well as the acute control Mania and severe bipolar disorder is well known.

Antipsychotics are used as antiemetics and in the palliative treatment of some movement disorders as Huntington and other chorea disorders. Tics that characterised the Tourette's syndrome also respond well to dopamine antagonists.

The more sedative action and lower incidence of extrapyramidal side effects with some AP are particularly indicated for the treatment of great psychomotor agitation, especially in situations of urgency and in a timely manner.

### 3.1.2 Side effects

The low-power typical antipsychotics, those that require higher doses to produce therapeutic benefits, tend to have more sedative, anticholinergic, and antihypertensive effects than the most powerful drugs. At the same time the latter tend to cause more extrapyramidal symptoms because of the antagonistic effect of dopamine on the dopaminergic nigrostriatal via.

The anticholinergic effects of less incisive drugs, or incisive at high doses, cause sometimes problems in elderly and heavily dependent patients, which may present difficulties in concentration, decreased performance, confusion and delirium. These effects are more intense in the early stages of treatment and generate some tolerance over time. On the other hand, the less powerful drugs have idiosyncratic reactions more often. For example, chlorpromazine can cause hypersensitivity to light or greyish skin patches requiring the preventive use of sunscreens.

**Extrapyramidalism:** Akathisia, a subjective sensation of motor restlessness and associated psychological discomfort, is the most common extrapyramidal adverse effect. It can appear at any time, being most common at the beginning of the treatment. Akathisia can improve decreasing the dose of the antipsychotic or associating with it a  $\beta$ -Blocker such as propranolol or a long-life benzodiazepine.

Acute dystonia is a short, sharp and painful muscle spasm that usually affects the face muscles, neck (retrocolis spasm), back (opisthotonos) and the extraocular muscles. This side effect usually affects young males who had not received prior treatment with antipsychotic medication. Dystonia is much more prevalent, the greater is the power of the drug. Symptoms usually improve managing anticholinergic drugs.

Tardive dyskinesia is a persistent syndrome in patients that keep treatment with antipsychotic drugs for prolonged periods. It is characterized by involuntary and repetitive abnormal choreoathetotic movements of the head, trunk and extremities.

Neuroleptic Malignant Syndrome is a very serious idiosyncratic reaction that appears hours or days after the initiation or augmentation of treatment with antipsychotic drugs. There are elevation of transaminases and lactate dehydrogenase (LDH). This syndrome involves a mortality approaching 30% being the most common causes of death, cardiac arrhythmias, secondary respiratory failure, aspiration pneumonia and renal failure for rhabdomyolysis. Bromocriptine has traditionally been used for mild cases and dantrolene intravenous for more serious cases

**Cardiac effects:** due to the action of the AP on the adrenergic  $\alpha_1$  receptors in the initial stages of the treatment may appear hypotension postural and tachycardia that tend to improve progressively with the time. The low-power APs may cause arrhythmia with widening of the QRS or QTc interval, polymorphous ventricular tachycardia and ventricular fibrillation.

**Gastrointestinal side effects:** due to the anticholinergic activity it appears dryness of mouth, nausea, vomiting and especially constipation that can even evolve towards ileus.

**Endocrine effects** of hyperprolactinemia: galactorrhea, menstrual disturbances, delays of ovulation and infertility, early reduction of bone density and osteoporosis, erectile

dysfunction and decreased libido. They can precipitate increase in weight and intolerance to the carbohydrates and diabetes

**Genitourinary effects:** urinary retention and difficulty in starting urination, secondary urinary tract infections.

**Hematological effects:** leukopenia, (in general, it is temporal and it is not severe), thrombocytopenic Purpura, hemolytic anemia and pancytopenia

### 3.2 Atypical or Second Generation Antipsychotics (SGA)

Clozapine produces a total blockade of D2 receptors, so it does not cause extrapyramidal symptoms. Properties of clozapine are due to the combination of a low affinity for the D2 receptors along with strong affinity to serotonergic 5HT<sub>2A</sub> and 5HT<sub>1C</sub>, adrenergic and cholinergic receptors. Clozapine joins less intensely this receiver, which is displaced by endogenous dopamine. This property is present in many SGA, not only clozapine, so these drugs cause fewer movement disorders as side effects

The indication of clozapine is the treatment of schizophrenia in patients who do not respond (after at least two months of treatment at appropriate doses) or that they do not tolerate the AP, although occasionally prescribed for other purposes such as the treatment of psychosis by L-DOPA in Parkinson's disease patients with mania. It can produce leukopenia, so it's important to control it weekly during the first six months of treatment and every fifteen days from then. However, it should be noted that this risk is low, less than 1%. Other adverse effects are: orthostatic hypotension and tachycardia, increased sedation, and the decline of the seizure threshold with the consequent risk of convulsions in 5-10% of cases. Some patients develop a symptomatic complex called metabolic syndrome which consists of weight gain, increased insulin resistance, increased risk of diabetes type 2, and elevation of plasma lipids. Clozapine may increase plasma levels of enzymes such as transaminases GOT and GPT (alanino aminotransferase and aspartate aminotransferase), alkaline phosphatase, gamma glutamiltranspeptidasa (GGT) and lactate dehydrogenase.

**Risperidone:** Its mechanism of action is mediated by its high affinity for D2 receptors, 5HT<sub>2A</sub> receptors and the adrenergic  $\alpha$ <sub>1</sub> and  $\alpha$ <sub>2</sub> receptors. Unlike haloperidol shows a low affinity for muscarinic receptors for which leads to fewer anticholinergic effects. With a similar effectiveness or even something greater than haloperidol, involves a greater tolerance, although risperidone at high doses can also cause extrapyramidal symptoms.

It is considered a SGA first line in the treatment of psychoses with particular effectiveness in the prevention of recurrences. It has been used in child psychiatry in the treatment of aggressive and serious behaviour disorders.

There is an increase in brain-vascular accidents in connection with the use of risperidone and olanzapine in elderly patients with dementia, a complication which advised the prescription of this drug with much caution in such patients.

There is a long-acting form of risperidone that can be used twice a month in injection for maintenance treatment.

Adverse reactions that occur more frequently with therapeutic doses of risperidone are sedation, orthostatic hypotension, tachycardia, increase in weight and erectile dysfunction,

hyperprolactinemia. At high doses anticholinergic effects such as dry mouth, constipation, changes in vision, and urinary retention may appear.

No significant pharmacological interaction with risperidone has been described what can be a great advantage in patients with a lot of pharmacological treatment, particularly in the framework of liaison psychiatry.

**Olanzapine:** its main indication has been the treatment of schizophrenia, acute episodes of mania and maintenance of bipolar affective disorder. Its structure is similar to clozapine and its mechanism of action is unknown, although it has a stronger affinity for the receptor 5HT<sub>2A</sub> than by the dopamine receptor D<sub>2</sub>. Olanzapine also acts at various levels, interacting with D<sub>1</sub> and D<sub>2</sub> dopaminergic, 5HT<sub>2A</sub> serotonergic, H<sub>1</sub> histaminergic, and muscarinic receptors.

Among his include anorexia nervosa, post-traumatic stress disorder and borderline personality disorder where, at low doses, it seems to improve objectives such as aggression and impulsiveness parameters.

Olanzapine is metabolized in the liver by oxidation and glucuronidation by cytochrome P450 isoenzyme 1A<sub>2</sub>. In smokers it must be important to adjust the dose, since the consumption of cigarettes induce 1A<sub>2</sub> isozyme and increases drug elimination.

The main adverse effect that occurs in patients in treatment with olanzapine is weight gain, so, an important risk that must be taken into account in relation to this and other drugs which produce significant weight gain is the metabolic syndrome. Other side effects of olanzapine are: sedation, elevation of prolactin, leukopenia (without agranulocytosis), and decrease the seizure threshold. Olanzapine carries a lower risk of episodes of Parkinsonism, dystonia and tardive dyskinesia.

**Quetiapine** has clozapine similar profile, with a moderate affinity to D<sub>2</sub> receptors and moderate-intense to 5HT<sub>2</sub> serotonergic receptors. It is a partial agonist of 5HT<sub>1A</sub> receptors, which increase dopamine concentrations in mesocortical area, improving cognitive and negative schizophrenics symptoms.

It produces few extrapyramidal symptoms and risk of tardive dyskinesia. These features make it the choice for the treatment of disorders of behavior in Parkinson's patients and patients treated within the framework of liaison psychiatry. Undesirable side effects are sedation and weight gain with alteration of glucose and lipid metabolism. However, it does not produce a significant increase in prolactin levels

Quetiapine is metabolized in the liver by the cytochrome P450 3A<sub>4</sub> enzyme, so drugs that produce a large inhibition of the isozyme (such as erythromycin) may increase their serum levels. Carbamazepine and phenytoin reduce levels of quetiapine as behave as enzyme inducers forcing adjust the dose to avoid possible relapse in patients who are simultaneously being treated with these drugs.

**Ziprasidone** has high antagonism of 5HT<sub>2A</sub>, 5HT<sub>1D</sub>, 5HT<sub>2C</sub> serotonergic and D<sub>2</sub> dopaminergic receptors. It has a low tendency to cause extrapyramidal effects because their high ratio 5HT<sub>2A</sub> / D<sub>2</sub> and its low affinity for adrenergic, muscarinic and histaminergic receptors.

Ziprasidone is metabolized in the liver by isoenzymes 3A4 of the P450, through a process of reduction effect of aldehyde oxidase. Its bioavailability increase when ziprasidone is administrated along with food. This compound intensely joins proteins and has not been shown to see displaced by other drugs with similar affinity.

In addition to the indication in the acute treatment and maintenance of schizophrenia, given that it exists in injectable presentation, you can use in patients who do not collaborate in the taking of oral medication and in emergency situations characterized by agitation or serious behavior disorders.

It is the antipsychotic with a lesser influence upon weight. The most frequent adverse effects are drowsiness, insomnia, constipation and nausea. Normally these effects tend to be temporary and, in general, ziprasidone is well tolerated.

**Amisulpiride:** While it has no affinity for subtypes D1, D4 and D5 presents affinity on the D2 and D3 of the dopamine receptor subtypes. Unlike other AP, it has no affinity for serotonergic, adrenergic, cholinergic and H1 histaminergic receptors.

An important feature that distinguishes it from other antipsychotic group is its low liver metabolism which must be taken into account within the framework of the psychiatric consultations when treating patients with liver failure that you do not need to adjust the dose. Their degree of plasma protein binding is low (around 16%). The drug is eliminated through the kidneys in 90% during the first 24 hours. In patients with severe kidney disease dosages should be reduced.

Adverse reactions that occur most often are: insomnia, anxiety and even turmoil psychomotor, which can appear at the beginning of treatment and declining thereafter. As with other antipsychotics the amisulpiride can reduce the seizure threshold, which requires a control of treatment in patients with a history of seizures. A reversible increase of plasma levels of prolactin can be seen. No drug interactions with this compound have been described so far.

**Aripiprazole:** This is a partial agonist of dopamine receptor D2, D3 and serotonergic 5HT1A and works as a 5HT2A serotonin receptor antagonist.

In some situations aripiprazole would act as an antagonist and in others as agonist. That way there would be a self-regulation of dopamine, so the drug would act as antidopamine at the mesolimbic via and as prodopamine at the mesocortical via, without significantly affecting the nigrostriada or the tuberoinfundibular paths.

Its theoretical advantages would be improvement in cognitive aspects and motor effects in the long term such as tardive dyskinesia. It is metabolized in the liver by isoenzymes of the cytochrome P450 3A4, and 2D6 so that compounds which interact at this level (carbamazepine, quinidine, ketoconazole, fluoxetine and paroxetine) could alter the plasma concentrations of aripiprazole. It is a well tolerated drug that does not affect significantly the weight or the levels of prolactin for patients, or metabolism of glucose and lipids. The most frequent side effect is drowsiness.

**Paliperidone:** It is an active metabolite of risperidone. It presents a great affinity for 5HT2A receptors and moderated by the D2 receptors, with a lower lipophilicity than risperidone. The pharmacological activity of this compound is similar to other high power

SGA. The receptor binding profile is similar to risperidone and ziprasidone, though unlike risperidone and other SGA it has a low rate of hepatic metabolism. Its adverse effects are similar to the risperidone although they produce a greater increase in the rate of hyperprolactinemia.

#### 4. Lithium and anticonvulsants

Although there is no agreed definition, stabilizer of the mood would be the drug with the potential to be used as monotherapy in acute bipolar disorder (BD) phases and its prophylaxis.

**Lithium:** Its mechanism of action is not clearly established, although it competes with other monovalent cations, such as sodium, altering metabolism and the action of certain neurotransmitters such as serotonin and Catecholamines.

**Indications:** bipolar and recurrent major depressive disorders. It has a narrow therapeutic range (between 0,60 and 1.5 mEq/L).

Contraindications Leukemia for possible reactivation.

**Side effects:** are frequent, could be severe and usually related to doses. Initial symptoms are nausea, diarrhea, abdominal pain, dizziness, muscle weakness, fine trembling hands. It can precipitate a renal Diabetes Insipidus (polyuria and polydipsia), which can lead to dehydration and increased toxicity. Hypothyroidism has been described in prolonged treatments, it is recommended to carry out periodic checks on the thyroid function. Other: increase in weight, swelling, leukocytosis, hypercalcemia due to hyperparathyroidism, hypermagnesemia.

**Interactions:** the thiazides may reduce renal excretion of lithium and may increase its toxicity. NSAIDs: reduce renal excretion of lithium and increase the risk of toxicity, particularly indomethacin. The analgesic of choice if needed would be ASA and acetaminophen. Carbamazepine: have described cases of serious neurotoxicity. ACE Inhibitors: can decrease renal excretion of lithium in patients of advanced age, renal failure or hypovolemia. Selective serotonin reuptake inhibitors: risk of serotonin syndrome.

**Valproate:** It facilitates the action of GABA, a neural inhibitor neurotransmitter, and as a result decreases neuronal excitability.

Indications Epilepsy, Infantile febrile convulsions, Bipolar disorder

It is postulated that there is a good correlation between the pharmacological effect and the plasma concentration, with a margin of optimal concentration of 50-150 mg/l. Some patients respond to concentrations outside this interval. Valproic acid is hepatotoxic.

Side effects are relatively frequent and usually transient or dose-related adverse effects. Gastrointestinal: nausea and vomiting, polyphagia with weight gain; rarely pancreatitis; increase of liver enzymes, hepatitis and hepatic encephalopathy syndrome (Reye in children), has described particularly in the first months of treatment. Nervous system: tremor and headache (usually the first sign of overdose), drowsiness, ataxia, confusion, dementia. Hematological: idiosyncratic depression of the bone marrow with thrombocytopenia, leukopenia and agranulocytosis, not related to the dose in nature. Skin: idiosyncratic character.

### Special situations

- Liver function: recommended a special control of high-risk patients, including the epilepsy with combination therapy, and evaluate the liver function before treatment and for at least every six.
- Discontinuation of treatment: the sudden suspension of the drug should be avoided because of the risk of seizures.
- Pregnancy: category D of the FDA. Isolated cases of defects of the neural tube in newborn infants, especially in women with combination therapy have been described. It has been observed that the incidence is higher than with other antiepileptic drugs. It is recommended to assess each case carefully, because the risk of the treatment is lower than the derivative of precipitate seizures. In any case, it is recommended to take supplements of folic acid before conception and during pregnancy to prevent these defects.
- Lactation: it is excreted in breast milk in a proportion that does not seem to pose risk to the infant. It is compatible, although some cases of thrombocytopenia associated with valproic in an infant has been described.

Interactions Carbamazepine, phenytoin, and Phenobarbital: the interaction is complex and unpredictable. Polytherapy recommends adjusting the dosage on plasma levels and the patient's clinical status. Lamotrigine: valproic increases lamotrigine plasma levels by inhibiting its metabolism. In addition, severe toxic reactions (rash, tremors) have been described. It is recommended halving the dose of lamotrigine.

**Carbamazepine:** It inhibits the voltage-dependent sodium channels of the CNS neurons, reducing neuronal excitability of the epileptic focus. It also has analgesic and antimanic properties.

**Indications:** Epilepsy, Trigeminal neuralgia, Bipolar disorder and potential use in impulsive disorder, addiction and personality disorders.

Hematological, hepatic, renal and cardiac functions and electrolytes should be explored before starting treatment. Plasma levels are: optimum plasma concentration 6 - 12 mg/L in monotherapy and 4 - 8 mg/L in combination therapy.

**Contraindications:** A history of depression of the bone marrow, Atrioventricular conduction disturbances, Porphyria due to risk of exacerbation of disease.

Adverse effects are relatively frequent (up to 50% of patients) and generally related to the dose.

- Nervous system: drowsiness, dizziness, headache, blurred vision and diplopia, nausea and vomiting, confusion and agitation (in older people).
- Hematological: idiosyncratic character, unrelated with the dose. Leukopenia, thrombocytopenia, agranulocytosis, and rare cases of fatal aplastic anemia has been occasionally described.
- Skin: idiosyncratic character. Regard rash, rarely Stevens-Johnson Syndrome.
- Other: hyponatremia, urinary retention, impotence, proteinuria, glycosuria, peripheral neuropathy, paresthesias, tinnitus, alopecia.

### Precautions

- Liver failure: increases the risk of toxicity because the drug is eliminated mostly by this route. It is recommended to carry out periodic checks on the liver function.
- Renal insufficiency: increases the risk of toxicity because the active metabolite is eliminated through the kidneys. It should adjust the dose according to the functional level.
- Heart failure: can worsen and cause arrhythmia and fluid retention.
- Blood disorders: increases the risk of aplastic anemia or agranulocytosis. It is recommended to carry out periodic checks on hemogram.
- Alcohol: it should be avoided because it induces hepatic metabolism of the drug and is epileptogenic
- Suspension of the treatment: the sudden suspension should be avoided because there is a risk of seizure.
- Pregnancy: category C of the FDA. Although isolated cases of abnormalities in newborns have been described, it is recommended not to suspend the antiepileptic treatment unless the risk of seizures is low, because the risk of the treatment is lower than the derivate of precipitate seizures.
- Breastfeeding: it is excreted in breast milk in a proportion that does not seem to pose risk to the infant. It is compatible, although at high doses there is risk of liver disease in infant.
- Geriatrics: it is recommended to use lower initial doses, usually half of it and adjust according to plasma level.

**Interactions:** With Phenytoin, valproic acid the interaction is complex, because both can induce the metabolism of the other. Occasionally neurotoxicity can appear with lithium.

**Oxcarbazepine:** It is a carbamazepine analog, and its indications are partial seizures with or without secondary generalization, bipolar disorder and other potential uses in psychiatry as carbamazepine.

### Side effects:

- Nervous system: frequently, drowsiness, headache, and dizziness. Also nystagmus, Vertigo. Occasionally ataxia, agitation, difficulty in concentration.
- Gastrointestinal: frequently, nausea and vomiting. Occasional constipation, diarrhea, and abdominal pain. Occasionally increase in liver transaminases
- Skin: rash, acne, alopecia.
- Eye: frequently diplopia, blurred vision.
- Hyponatremia: it can be severe, especially for elderly, renal failure or treatment with diuretics.

### Special situations:

- Suspension of the treatment: the sudden suspension should be avoided because it can cause seizures.
- Pregnancy: category C of the FDA. Malformations in animals have been described but there is no information in humans.
- Breastfeeding: Oxcarbazepine and its active metabolite are largely excreted in breast milk. Although the effects on the infant are unknown, its use is not recommended.

- Renal insufficiency: half of the initial dose is recommended in case of serious failure and then adjust the dose more slowly

**Lamotrigine:** It reduces the excitability of neuronal inhibitor dependent sodium channels and blocks the release of glutamate. Its indications are epilepsy, Lennox-Gastaut syndrome and bipolar disorder

**Side effects:** They are relatively common, while in most cases these effects are minimized if the dose is gradually increased. It can produce headache, dizziness and drowsiness; nausea and vomiting, and abdominal pain; diplopia, nystagmus, arthralgia, sore back, depression of the bone marrow (anemia, leukopenia, thrombocytopenia and associated infections) and dysmenorrhoea.

Special situations:

- Liver failure: increases the risk of toxicity because the drug is eliminated mostly by this route. Initial and maintenance doses should be reduced typically in moderate failure to 50% and 75% in the event of serious failure.
- Pregnancy: cat.C of the FDA. There has been an increase in the risk of oral fissure.
- Lactation: excreted in milk, can reach therapeutic concentrations in the infant.

**Gabapentine:** It is structurally similar to GABA with antiepileptic and analgesic action. It facilitates neural inhibitory action of this neurotransmitter, and consequently decreases the epileptic crises responsible of neuronal excitability. It is eliminated by renal excretion with a half-life of 5-7 hours, unlike traditional antiepileptic, eliminated by hepatic metabolism.

Special situations:

- Renal insufficiency: due to it is removed by this way, it is important to adjust the dose to the functional level.
- Special activities: the onset of drowsiness and dizziness before driving or operate dangerous machinery must be controlled.
- Pregnancy: category C of the FDA.
- Lactation: it is excreted in breast milk but unknown effects on the infant. Caution is advised.

**Topiramate:** It inhibits the voltage sodium dependent channels implicated in the spread of the epileptic focus, it reduces the excitatory action of glutamate. It is eliminated by renal excretion with a half-life of 20-24 hours.

**Indications:** Epilepsy in adults and children (monotherapy or combination therapy), Lennox-Gastaut syndrome, in combination therapy. Migraine prophylaxis in patients. Bulimia with overweight and alcoholism, binge disorder and bipolar disorder

**Side effects:** are frequent but generally moderate. They can be minimized by gradually increasing the dose and usually resolve spontaneously over treatment or when the dose is reduced. Nervous system: 10-30% of patients can suffer from fatigue and sleepiness and paresthesias at the beginning of treatment, although they are not usually serious. It also produces ataxia, nervousness, confusion, loss of concentration, anxiety, depression, cognitive disturbances. Visual: the first month of treatment may be acute nearsightedness, diplopia and/or nystagmus, not related to the dose, which can lead to glaucoma.

Gastrointestinal: abdominal pain, nausea, anorexia, taste alterations, gingivitis. Other: anorexia and weight loss associated with a diuretic effect (very common) and nephrolithiasis.

**Special situations:** there is risk of formation of nephrolithiasis in patients with antecedents. It is necessary to maintain adequate hydration during the treatment. As it is excreted through the kidneys, in renal failure doses must be reduced up to 50%.

**Pregabalin:** It is structurally similar to GABA, with antiepileptic, anxiolytic and analgesic action. It facilitates neural inhibitory action of this neurotransmitter and consequently decreases the epileptic crises.

**Indications:** Treatment of adult central and peripheral neuropathic pain. Epilepsy in adults: combined treatment of partial seizures with or without secondary generalization. Anxiety disorders in adults.

## 5. Benzodiazepines

Benzodiazepines (BZD) are CNS depressors with anxiolytic and hypnotic-sedative properties, and antiepileptic and muscle relaxing effects. They are more secure in overdoses than barbiturates and other sedative drugs. They have similar action mechanism and side effects, and differ in onset time and activity duration, which is relevant in treatment and indications.

Absorption in the gastrointestinal tract is very good, especially on an empty stomach, so that the oral via is the choice for these agents. Diazepam and clorazepate are absorbed more quickly than the others. Other routes of administration are less recommended and should be reserved only for cases of urgency: the intramuscular absorption is erratic and intravenous absorption can be dangerous. The BZD are lipophilic agents, so cross the blood-brain barrier well, exerting their action at the level of the central nervous system quickly. They also cross the placental barrier and are excreted through breast milk. Furthermore, their solubility makes that most of them are accumulated, gradually, in body fat resulting in a high volume of distribution, which directly influences the duration of the action.

The biotransformation is at hepatic level through a process of oxidation and conjugation. Some BZD (such as the diazepam or clorazepate) have pharmacologically active metabolites which, sometimes, even have longer life than the active ingredient.

In addition, should take into account that in the healthy elderly these processes are altered, so you have to choose BZD not metabolized by microsomal liver enzymes and without active metabolites as oxazepam or lorazepam. They are eliminated on a majority basis through the kidneys (70-90%), after their hepatic metabolism. The rest are eliminated through the stool or bile.

All BZD's action is at CNS, by their ability to enhance the inhibitory actions of GABA, stimulating the GABA-A receptor. It is believed that their anxiolytic action is due to the inhibitory action on neurons in the limbic system, including the amygdala, and serotonergic and noradrenergic neurons of the CNS. The fact that ethanol, barbiturates, and BZD have similar actions on the same receptor explains their drug synergy (and therefore the danger of the combined overdose) and its cross tolerance. This last property is used in the detoxification of alcoholics with BZD.

### 5.1 Other hypnotics/anxiolytics agents

**Zolpidem, zopiclone and zaleplon:** Three non-benzodiazepinic preparations that interact with a smaller subset of receptor GABA-A (type 1), therefore presenting crossed reactivity with these to some extent. It seems that by their more selective binding, they are effective for short-term insomnia treatment, but they lack significant muscle relaxing, anti-epileptic and anti-anxiety effects. They have lower risk of dependence and abstinence than BZD.

**Buspirone:** It is believed that it exerts anxiolytic effect acting as a partial agonist of the 5-HT<sub>1A</sub> receptors (of serotonin). Its advantages include the absence of induced physical dependence and withdrawal, does not interact with alcohol or other CNS depressants, has no sedative effect and amnesic, does not diminish the psychomotor performance and not depressed respiration (being useful in the elderly and patients with respiratory problems). Its main drawback is the delay in the onset of the anxiolytic effect (up to 2 weeks) and its ineffectiveness in patients previously treated with BZD.

### 5.2 Adverse effects and contraindications

The most frequent adverse effects are: drowsiness, sedation and psychomotor performance. Anterograde amnesia is associated with the use of more powerful BZD. Very rarely allergic reactions or a paradoxical increase in aggressiveness have been described. They can produce respiratory deficiency in patients with chronic obstructive pulmonary disease or sleep apnea. They should be administered with caution in patients with substance abuse, liver disease, kidney disease, Porphyria, depression from CNS or myasthenia gravis. Despite being one of the tools most often used in cases of suicidal ideation, Benzodiazepines alone are relatively safe in overdose (especially as compared with other sedatives like barbiturates). In addition, the fact of having selective antagonists of the benzodiazepinic receptor, such as Flumazenil, limited the dangerousness of these poisonings. The most dangerous effects occur when administered concomitantly with other sedatives such as alcohol (in these cases can occur excessive sleepiness, disinhibition and respiratory depression, as well as severe cognitive deficits).

Buspirone, zolpidem, zopiclone and zaleplon can produce nausea, dizziness and headaches, and except the first, others can also produce drowsiness and certain anterograde amnesia.

There are few absolute contraindications for BZD: allergic reactions to the drug and angle closure glaucoma. Other related are: severe apnea sleep, first trimester of pregnancy, respiratory failure and cognitive disorders.

### 5.3 Tolerance and dependence

All BZD may exhibit properties of tolerance and dependence. However, there is to be noted that they do not constitute a group of drugs of addictive nature, as with the characteristics of drugs of abuse have no place tolerance is defined as the increasingly low intense effects production, maintaining the same dose of drugs. The use of BZD at long term can cause a phenomenon of tolerance to their pharmacological effects, it is clearer to the hypnotic, sedative effect and impaired psychomotor performance (1-2 weeks tolerance). On the other hand, tolerance to the anxiolytic effects and mnesic is very unlikely, and when it appears, at very late onset.

Most anti-anxiety agents give after their sudden suspension, a series of symptoms of withdrawal or "deletion syndrome" which usually correspond to the image in mirror of its therapeutic effects

## 5.4 Clinical indications

Anxiety, insomnia, depression, alcohol deshabituatio. Although Benzodiazepines are marketed for other indications (such as fluracepam, temacepam or triazolam for insomnia, or diazepam for anxiety) is likely all drugs of this class to share most of their therapeutic properties. The indications for which they are adopted reflect many times commercial decisions rather than a rational therapeutic. It is best to choose the drug based on differences in pharmacokinetic and power.

## 5.5 Special situations

**Pregnancy and breastfeeding:** BZD cross the placental barrier and GABA is involved in the reorganization of the massif of the palate. There are studies in which there has been an increase of teratogenia in pregnant women treated with chlordiazepoxide during the first quarter and retrospective studies and cases in which noted an increase in risk of cleft palate and cleft lip associated with the use of BZD by the mother.

- Syndrome of the hypotonic newborn: depression of the CNS, with hypotonia, lethargy, weak suction and respiratory depression.
- Neonatal abstinence syndrome: hyperactivity, irritability, and hypertonia.

BZD are excreted in breast milk. Infants metabolize them slowly, so it is possible the accumulation and toxicity, with lethargy, feeding difficulty and weight loss as well as withdrawal symptoms in the infant. For this reason, and despite the fact that the plasma/milk proportions are low in some BZD is necessary the evaluation of risk-benefit from the establishment of breastfeeding. In case of need for treatment BZD in postpartum period, as a general rule will be necessary to resort to artificial feeding.

**Elderly:** There is the need of a special caution in the treatment with BZD in this population due to there is increased sensitivity to the pharmacological action, there are deficiencies in the hepatic metabolization (reducing the reactions of phase I: oxidation) and possible decreases in renal elimination, increase in the amount of free medication for decrease in plasma proteins, increase in the volume of distribution with the possibility of accumulation. These cause an increase in side effects in this population: sedation, cognitive alterations and decline of the alert. There is an increase in the risk of falls and fractures and an increased risk of suffering from delirium, especially in treatments with long half life BZD. It is recommended a reduction of 30 to 50% of the doses, and the use of short half life BZD that are metabolized in phase II (glucuronidation) as oxazepam and lorazepam.

**Children and adolescents:** There are few studies of effectiveness/security in concrete disorders, and there is risk of abuse/dependence and paradoxical reactions.

**Liver insufficiency:** Liver failure affects mainly the metabolic processes involving the cytochrome P450. So, there have been significant increases in the half-life of diazepam, chlordiazepoxide and its metabolites. Also, the metabolism of alprazolam, clobazam and diazepam and midazolam is affected significantly in cirrhosis, it would be advisable to drop doses in these BZD. BZD who suffer processes of glucuronidation (lorazepam, oxazepam and temazepam) are little affected in liver failure, being at low doses the choice treatment. Patients with liver failure are more sensitive to the sedative effects of BZD, and these may precipitate hepatic encephalopathy, so they are contraindicated in cases of serious-preencefalopatic liver failure and hepatic encephalopathy.

**Renal failure:** When treating with BZD patients with renal failure is necessary to take into account: the degree of renal failure, the existence of active metabolites, whose clearance may be diminished and binding to plasma proteins. To avoid this risk, is preferable to the use of BZD without active metabolites in low doses.

**Respiratory failure:** The BZDs, due to its CNS depressant effect, can reduce ventilatory response to hypoxia, so they must be used with caution in patients with COPD and are contraindicated in sleep apnea.

**Porphyria:** The hepatic metabolism of BZD may enhance the synthesis of ALAsintetasa, giving rise to an increase of Porphyrin with exacerbación of the disease.

**Dementia and delirium:** Action on the CNS of BZD has been linked to cognitive impairment and their use in patients with dementia can precipitate delirium, so, as far as possible, it's better to avoid their use, being preferable to the use of antipsychotics in low doses. In delirium, except for the secondary to abstinence from alcohol or benzodiazepines, it is necessary to avoid the use of BZD, especially those of long half life, as they may aggravate the confusional syndrome.

**Interactions:** The main pharmacodynamic of BZD interactions occur with central nervous system depressant drugs (opioids, barbiturates, anticonvulsants, anesthetics, tricyclic antidepressants, central antihistamines, MAOIs, antipsychotic drugs and alcohol). In combination with these drugs, there is a strengthening of the depression of the CNS, which increased sedation, impaired psychomotor and respiratory depression.

Pharmacokinetic interactions are those related to the absorption, fixation to plasma proteins, metabolism and excretion. BZD requiring metabolization by reactions of phase I are influenced by processes of inhibition and metabolic induction, unlike BZD who suffer glucoronización are hardly influenced.

## 6. Drugs used in opioid addiction: Methadone

Methadone is an opioid analgesic with an outstanding action on the mu receptor. In cases of opioid dependence methadone is useful for treatment of detoxification, maintenance, and harm reduction.

**Side effects:** The most frequent are nausea, vomiting, constipation, sweating, sedation, euphoria, dependency and respiratory depression. In addition, it has a special impact effects on sexual function (decreased libido, decrease of serum levels of testosterone in men) and endocrine (deficit of production of ACTH and subsequent secondary hyposuprarrenalism cases). Other less common but important side effects are: urinary retention, agitation, drowsiness, headache, disturbance of sleep, confusion and psychotic symptoms.

**Special situations:** Opioid analgesics are generally contraindicated in acute respiratory depression, obstructive respiratory processes and patients in treatment with opioid antagonists (naltrexone). They are also contraindicated or should be used with great caution in alcoholism, seizure disorders, head injuries and processes that have increased intracranial pressure. They must not be administered to patients in a coma. In patients with biliary disorders it's usually recommended to avoid the use of opiates. Opioid analgesics should be administered with caution or dosage reduced in patients with: hypothyroidism, adrenocortical insufficiency, asthma, or decreased respiratory reserve, kidney or liver

failure, prostate hyperplasia, hypotension, shock, inflammatory or obstructive intestinal disorders and myasthenia gravis. The dose should be reduced in elderly or debilitated patients. Methadone can prolong cardiac QT interval, increasing the risk of torsades de pointes, which implies risk of sudden death.

## 7. Stimulants

It is a group of drugs that in addition to its use in hyperactivity (ADHD) and attention deficit disorder have been used in the treatment of resistant depression, and narcolepsy.

Amphetamine is a sympathomimetic which facilitates the release of NA and dopamine. It has a strong stimulatory effect on the central nervous system (CNS), particularly with regard to the cerebral cortex

**Side effects:** The most frequent are anxiety, agitation, and decrease in sleep. Sometimes, dry mouth, anorexia, colic and other gastrointestinal discomfort. They can also lead to headaches, dizziness, tremors, sweating, tachycardia, palpitations and elevation (sometimes decrease) of blood pressure. Serious adverse effects such as psychosis, arrhythmias, hyperthermia, rhabdomyolysis, and seizures, especially with toxic doses that in some cases are not necessarily high are described. There is reasonable evidence that stimulant medication, especially at high doses, inhibits growth moderately. There are indications of that part of the growth is recovered when the treatment is interrupted.

**Special situations:** It is contraindicated in patients with cardiovascular disease, including hypertension moderate to severe, and in patients with hyperthyroidism, glaucoma, psychosis, or states of agitation. It is more likely abusive consumption in patients with a history of alcoholism or drug addiction. Amphetamines can trigger symptoms in patients with tics or Gilles de la Tourette syndrome.

**Methylphenidate:** Methylphenidate is a stimulant of the central nervous system and an indirect sympathomimetic (inhibits the reuptake of norepinephrine and dopamine) with the same indications as dexamfetamine. It is indicated in Narcolepsy, ADHD and Treatment-resistant depression. The most frequent adverse effects are similar to amphetamines.

**Modafinil** is a "wakefulness Enhancer compound". It selectively activates the hypothalamus areas that regulate the vigilia-sueño cycle, although the exact mechanism of action is not known. It is indicated in narcolepsy, excessive daytime sleepiness adults, in ADHD improves attention and impulse control. Adverse effects on the CNS may give rise to nervousness, excitement, irritability, insomnia and anorexia, which rarely require the removal of the treatment. Also it has been associated with gastrointestinal disorders, such as nausea and abdominal pain, dry mouth, headache, and cardiovascular effects such as hypertension, palpitations and tachycardia. Modafinil is contraindicated in patients with hypertension of moderate to severe cardiac arrhythmias, it is not recommended in patients with a history of left ventricular hypertrophy or coronary alterations of the EKG, chest pain and prolapse of the mitral valve.

## 8. Non-stimulant treatment of ADHD

**Atomoxetine** is a selective inhibitor of the reuptake of norepinephrine used in the treatment of the attention deficit and hyperactivity disorder in adolescents and children from 6 years.

Adverse effects described in patients in treatment with Atomoxetine include dyspepsia and other gastrointestinal disorders, anorexia and weight loss, fatigue, disturbances of sleep, irritability, and mood swings. Also hypertension, tachycardia, dizziness, cough, sinusitis or runny nose, bed wetting or urinary retention, decrease of libido and sexual dysfunction, rash, increased sweating and hot flashes. Rarely, hypersensitivity reactions occur. There have been some reports of serious hepatotoxicity. Atomoxetine is contraindicated in patients with glaucoma. It should be used with caution in patients with hypertension, tachycardia, or cerebrovascular or cardiovascular disease. Treatment with Atomoxetine should start with caution in patients with a history of seizures. There is a potential risk of seizures with Atomoxetine.

## 9. Special situations

### 9.1 Psychiatric drugs in pregnancy and lactation

All psychotropic so far studied cross the placenta, most reach the amniotic fluid and almost all are eliminated through breast milk. 3-5% of the newborns have genetic malformations; 65-70% by unknown factors, hereditary factors 12-25%, 10% by environmental factors (drugs, infections, diseases...) and 3% by direct exposure to drugs. Most studies suggest that the psychotropic drugs are not associated with a significantly increased risk of organic disgenesias. Congenital anomalies are not more frequent in a group of regular consumers of drugs compared with a control group. Perinatal mortality was similar in both groups (0.8% and 0.9%). It is essential to inform the patient of the potential risks of medication, obtain the informed consent of the patient, taking into account the ability and desire to tolerate the symptoms without drugs.

Absortion	Metabolism
Decrease in the rate of gastric emptying. Reduction of intestinal motility.	Increase in cardiac output. Changes in the activity of various liver enzymes
Distribution	Elimination
Increase of blood flow in the tissues. Increase in plasma volume. Increase in the extracellular fluid volume. Increase in adipose tissue (nearly all psychotropic are highly fat-soluble). Changes in the concentration of some plasma proteins.	Increase in the renal blood flow. Increased glomerular filtration rate.

Table 1. Changes in drug metabolism during pregnancy

The prescription of psychoactive drugs only must be made if the benefit (to mother) is greater than the risk (to the fetus). If possible, avoid all drugs (especially during the first trimester of pregnancy) and managing the minimum effective dose. It is preferable to use drugs already tested with good safety profile, than new drugs, with a theoretical more secure profile but not tested. Smaller than 1,500 molecular weight drugs can cross the placental barrier and potentially affect the fetus, but few have demonstrated teratogenic effects. It is important to provide contraceptive information to women in chronic treatment and review the treatment early in the pregnancy.

Due to changes in pharmacokinetic and pharmacodynamic factors during pregnancy, often different doses are needed (may be higher or lower) than in normal conditions to treat the symptoms properly.

The intensity of fetal exposure to the psychotropic also depends on the placental transference: Type I or complete transference: the concentrations are quickly balanced between maternal and fetal compartments; Type II or excessive transference: Fetal drug concentrations are higher than the maternal ones; Type III or incomplete transference: Fetal concentrations are lower than the maternal ones.

## 9.2 Elderly

General elderly people have a health more fragile than other stages of life. They suffer from various diseases and receive different treatments, which leads to higher risk of adverse reactions. As a result of this overlap pharmacokinetics and pharmacodynamics changes in this age group and responses to treatments are different. Variations in therapeutic response and side effects and interactions, which are more frequent and more serious, result in more iatrogenia and worst compliance.

Interactions in the elderly, drug interactions are between 3 and 5 times more frequent than in other stages of life. The elderly modifies the absorption process. Esophageal motility is reduced. The achlorhydria increases with age. Gastric motility and intestinal irrigation are reduced. But, in general, all these changes in the absorption are not very relevant from a clinical point of view.

The majority of psychoactive drugs, except lithium, are lipophilic and go preferably to fatty tissue, including the brain. With age, albumin decreases and increases the proportion of free drug, increases the fat mass generally between 25-40%, it's reduced lean mass and the proportion of body water, especially with relative increase in the extracellular intracellular water, which increases the volume of distribution of soluble drugs and decreases of the water-soluble. Clinically the relevance is moderate but it can extend drugs half-life.

Old age significantly modifies the metabolism by loss of hepatic mass, decreased blood flow, lower microsomal enzyme activity and tendency to prolong the half-life. From the age of 65, hepatic perfusion is reduced in about one-third.

With age, glomerular filtration and hepatic metabolism are reduced which leads to increase drug concentration and, consequently, increasing the therapeutic and toxic effect. It can be compensated reducing the dose or spacing this. Drugs with long half life tend to accumulate.

Elders suffer almost always several concomitant pathologies so they receive the respective treatments. The majority of clinical trials have been developed in younger people. Receiving different products makes pharmacokinetic and pharmacodynamics interactions more frequent. It is common that an older person receives at least 6-8 drugs a day, each with its corresponding mechanism of action, side effects that join or therapeutic effects to be antagonized. In addition, it's not exceptional self-medication through acquaintances or relatives, with increased risk.

The frequency of adverse reactions is doubled in the elderly with respect to those that occur among adults and its severity is much greater. The greater is the number of drugs received,

higher is the risk. In elderly the most frequent adverse reactions are acute confusional states, psychomotor agitation, instability and falls, extrapyramidal symptoms, constipation or incontinence, anticholinergic symptoms, orthostatic hypotension or impaired heart function. If these factors are not taken into account, the yatrogenia among the old can be high and with unpredictable consequences.

### 9.3 Psychopharmacology in children and adolescents

The decision to use a pharmacological treatment in a child or adolescent with psychiatric disease should be based on a clear clinical need. Prepubescent children often metabolize drugs rapidly and tolerate doses of drugs per unit weight slightly higher than the adult. After puberty, metabolism seems to young adults. In general if a drug is safe in adults, it will be also in children. The period of maximum drug vulnerability is in the intrauterine stage. The majority of psychoactive drugs have not been approved by the FDA for use in children and adolescents, mainly because there are no studies to support it.

1. Psychiatric diagnosis must be made before the prescription of psychotropic drugs.
2. Define clearly target symptoms and the goals of treatment for the use of psychotropics
3. The doctor should carefully consider the possible side effects, including those which are rare but potentially serious, and assess the overall benefits from the risk of pharmacological treatment except in cases of urgency.
4. Informed consent must be obtained before starting medication psychotropic
5. Monotherapy wherever possible
6. Doses must be, in general, low and when it's necessary to increase, do it carefully.
7. The frequency of doctor-patient follow-up should be appropriate according to the severity of the pathology and must comply with to control the response.
8. In the treatment of depression, it's important to assess the possibility of that emerge suicidal tendencies during the treatment, especially at the beginning.
9. If who carries out the prescription is not a child psychiatrist, the patient must be sent for consultation specializing in child and adolescent mental health.
10. Before adding other psychotropic medications, it should be evaluated the proper adherence to treatment, the accuracy of the diagnosis, the emergence of comorbid disorders, and the influence of psychosocial stressors.
11. If a drug is being used for a symptom not associated to a diagnosis of psychotic disorder in DSM IV, and this symptom has been in remission for six months, it should be considered seriously to initiate the reduction and subsequent suspension of the drug. If you decide to continue with treatment, the need of it should be evaluated at least every six months.
12. The clinician must clearly document the care provided in the medical record, including medical history, mental status evaluation, physical findings (when appropriate), the diagnostic impressions, a proper follow-up of laboratory tests to rule out use of substances and the potential known risks, response to medication, presence or absence of side effects, treatment plan and prescribed medications.

## 10. Hepatic failure

With the notable exception of the lithium the liver is the responsible for the clearance of the majority of psychoactive drugs, as they are generally lipophilic and therefore need to be transformed into water-soluble compounds so that they can be filtered and eliminated by the

kidney. This transformation takes place largely in the liver, but also occurs to a lesser extent in other tissues. The inactivation is carried out by the large number of enzymes available in hepatocytes, which are responsible for reducing the size of the molecules or to add components to turn them into more hydrosoluble, with the final result of an easier elimination.

Due to the anatomical arrangement of the blood circulation of the gastrointestinal tract, absorbed drugs cross the liver before entering the general circulatory system. On some occasions, originated substance is an active metabolite, although the level of activity can vary widely. This effect called "first step" at times is very significant. This phenomenon also helps explain why parenteral medications are often more powerful than the oral equivalent. For example, antipsychotic drug intramuscular administration has approximately twice the power of those administered by mouth, although this varies widely from patient to patient.

The greater the degree of liver failure, greater degree of alteration of metabolism, and therefore, higher risk of toxicity from drugs. As a result, it is convenient to use possible smaller start dose, gradually setting it up to a maximum dose as low as possible. Patients are going to suffer more readily predictable or frequent adverse effects. Liver function tests do not necessarily correlate well with the deterioration of the metabolism, although they can serve as a reasonable approximation. It is important to be very careful with drugs with a high first pass metabolism, which in case of liver disease will be a minor inactivation during transport from the intestine to the circulatory system and therefore will be far higher plasma levels. As a general rule, avoid drugs that have marked effects like constipation and sedation in patients with severe liver disease. Monitor - wherever possible - the plasma levels of the drugs used

## 11. Renal failure and psychoactive drugs

If the drug is dialyzable, such as lithium, it will experience a sharp decline in its blood levels after dialysis, so post-dialytic of such drugs levels should be obtained to determine what amount is provided after the process. Certain drugs that are metabolized / eliminated by the kidney will accumulate, with the risk of toxicity, despite not using high doses of these, so that such drugs should be avoided or give at lower doses.

In general, the doses to be used will be two-thirds of the usual doses of the drug, except drugs with primarily renal elimination, in which will have to evaluate the clearance of creatinine (ClCr) as an indicator of renal function and the dose to use of the drug. Plasma levels of the drug in question must be controlled, at least once a month, and immediately after the initial dose of medication must provide wherever possible.

In renal failure protein binding is lower than in healthy individuals, so usually there is a greater amount of free drug in plasma, with higher therapeutic and side effects. The higher protein binding, the lesser dialyzable is the drug, what it's important to prescribe lower doses. In general, the most of the psychotropic substances aren't dialyzable, except lithium, gabapentine, pregabaline and others.

## 12. Cardiopathy and arterial hypertension

Antidepressant in cardiac illness must be used in therapeutical efficient doses, not lower doses, because metabolism is not affected if there is no hepatic afectation. Tricyclic antidepressants have severe cardiac side effects, so they have to be avoided if there is not a

clear indication, monitoring EKG frequently. Venlafaxine can increase arterial tension in high doses. SSRIs, bupropion and mirtazapine are secure in cardiac patients. Stimulants have to be avoided due to cardiac effects.

Lithium can produce sinoatrial node dysfunction and can be altered if there are rapid alterations of electrolyte equilibrium. Carbamazepine has quinidine-like effects.

Antipsychotic drugs can prolong QT interval and produce orthostatic hypotension, and new substances can induce diabetes mellitus type II and weight gain.

### **13. Pneumology**

Main pharmacologic interactions in patients with respiratory illness are those that appear between rifampicine and theophiline, and psychotropic drugs.

Benzodiazepines produce relaxation on respiratory vias and reduce the air pass, so they are contraindicated in sleep obstructive apnea and in chronic restrictive pulmonary illness. Zolpidem is the hypnotic drug with less effect on respiration.

There are some drugs used in pneumologic illness that have been related to psychiatric syndromes, as corticoides, diuretics, beta-blockers or central action antihypertensives.

### **14. Obesity and diabetes**

When treating a patient suffering from morbid obesity, diabetes or organic pathology which could be descompensated with weight gain, the drug must have little effect on weight. It is recommended to use SSRIs or noradrenergic with little effect on weight and watch for possible hypoglycemias that could need adjusting antidiabetic drug. Avoid MAOIs and heterocyclic antidepressants. Clozapine and olanzapine promote weight gain and can precipitate diabetes. Risperidone and quetiapine produce lower weight gain and occasionally diabetes. Aripiprazole and ziprasidone don't alter weight and don't produce metabolic syndrome. When a patient with overweight, obesity, prediabetes, diabetes or diabetes risk factors is receiving any psychoactive drug, it's important to monitorize laboratory analysis, arterial tension, and weight, at least basal, every three months the first year and then yearly.

### **15. Oncology**

In the treatment of patients suffering from cancer or in a final stage of the illness, the pharmacological prescription has to be accurate to physical state secondary not only to symptomatology related to cancer but to treatment too. In general, it's better to use drugs without active metabolites, without hepatic metabolism, well known drugs, without anticholinergic side effects (due to addition to cancer treatment ones) and with a good side effects profile. Though these considerations, psychiatric symptoms must be treated when appear in association to opioid analgesia if there is pain. In many cases the treatment with stimulants and antidepressants if there is depression is more efficacy than antidepressants alone, with a low risk of dependence. Zolpidem and zopiclone can produce metallic taste, so they must be avoid in cancer patients.

## 16. AIDS

There is risk of a poor tolerance, especially with high potency antipsychotics in the final stages of AIDS, due to extrapyramidal effects. Risperidone seems to have low interactions profile with drugs used for the infection. Agranulocytosis risk can be increased in treatment with clozapine. To treat depression it is recommended the use of citalopram, escitalopram and sertralina due to the lower risk of interactions (especially with ritonavir), though a serotonergic syndrome can appear. There are sparse and poor evidence of interactions with other antidepressants. Oxazepam, lorazepam and temazepam are anxiolytic choice treatment, due to their short half life, their metabolism and low profile of interactions. Lithium provokes frequently side effects. When using anticonvulsants as mood stabilizers, it's important to monitorize liver function. Stimulants can be used with a good profile of security and tolerance in patients with cognitive deterioration and depression.

Many drugs used in HIV infection treatment precipitate psychiatric symptoms (depression, anxiety, and insomnia). It is frequent the use of illegal drugs that interfere with treatment and can produce symptoms too.

## 17. Delirium

Treatment of delirium may complicate evolution of it, so it's important to select drugs with little sedative and anticholinergic effect, if possible one only drug, starting at low doses and during a short time, maintaining non-pharmacological measures (soft light, orientation, treatment of basal physical state...). The treatment is based in the use of antipsychotics, except in alcohol abstinence, where benzodiazepines must be used. Haloperidol is the choice drug, though there is little evidence about the usefulness of atypical antipsychotics. Benzodiazepines must be avoided because can cause a paradoxical effect with an increase of agitation.

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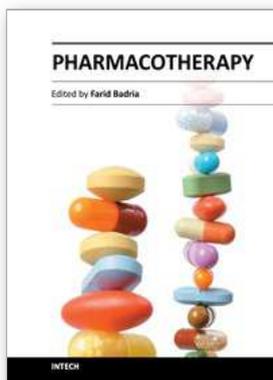
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## **Pharmacotherapy**

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The intent of this book is to provide an overview of current conceptualizations of Pharmacotherapy. The book focuses on three major areas; diagnosis, treatment, and prevention for a wide array of diseases; Cognitive and Psychological disorders (Schizophrenia and Nicotine addiction), Inflammatory disorders (New Chemical anti-inflammatory and Immunotherapy), updated antihypertensive therapy and healing of ulcers with venous origin. A separate chapter is dedicated to the rationality of drug use in earthquake injuries. The last chapter deals with Imaging of potential therapeutic or diagnostic agents in animal models in the early stage of research. We hope this book is useful to a wide range of people, from students first learning about Pharmacotherapy, to advanced clinicians and researchers.

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