Chapter 11

Psychopharmacology

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Abstract

Psychopharmacology is the scientific study of the effects drugs have on mood, sensation, thinking, and behavior. Particularly it concerns the use of medications in the treatment of mental disorders.

The goal of this chapter is to define the major classes of psychotropic drugs, introducing general pharmacological concepts, explaining the different mechanisms of action and the main clinical applications of the drugs used to treat psychiatric disorders.

Psychotropic drugs are commonly categorized according to their major clinical applications: antidepressants, anxiolytics, antipsychotics, and mood stabilizers. However, almost every drug used in psychiatry has multiple therapeutic roles and many clinical applications. For example, SSRIs are considered the first-line pharmacological treatment for several disorders, such as depressive disorders, anxiety disorders, and OCD. Similarly, antipsychotics are indicated as first-choice drugs for psychotic disorders, but many guidelines recommend their use, in combination with mood stabilizers, also in the treatment of acute mania.

Keywords: Antidepressants, Antipsychotics, Anxiolytics, Sedatives, Mood stabilizers

11.1. ANTIDEPRESSANTS

Introduction

Antidepressants, medicines originally used to treat depression, are nowadays FDA approved as a treatment in adults for a great variety of disorders such as depression, major depressive disorder, as adjunct therapies for bipolar I or II disorder, obsessive-compulsive disorder, bulimia nervosa, panic disorder, social anxiety disorder, generalized anxiety disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, fibromyalgia, chronic musculoskeletal pain, seasonal affective disorder, smoking cessation, insomnia.

Antidepressants are mostly prescribed for psychiatric diseases, but many non-psychiatric conditions benefit from the use of these agents: for example, insomnia, chronic pain, smoking cessation, Parkinson's disease, and vasomotor symptoms of menopause.

Antidepressants can be divided in classes according to their pharmacological profile. We'll focus on the most widely used drugs in clinical practice, providing an overview over less used molecules, that may be a starting point for further study.

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)
- Tricyclics and Tetracyclics (TCAs)
- Monoamine Oxidase Inhibitors (MAOIs)
- Other antidepressants (agents that do not fall into any of these classes and have peculiar mechanisms of action)

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) are nowadays the most widely prescribed antidepressants in clinical practice due to their effectiveness and few side effects compared to other classes of antidepressants.

The first SSRI fluoxetine (Prozac) was introduced in 1988, and, nowadays, other five molecules are marketed: fluvoxamine, paroxetine, sertraline, citalopram, and the most recent escitalopram.

SSRIs have received approval from the FDA as safe and effective in the treatment of a wide range of disorders: major depressive disorder, panic disorder, generalized anxiety disorder, social anxiety

disorder, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), premenstrual dysphoric disorder (PMDD), and bulimia.

Pharmacokinetics

An important Pharmacokinetics variability can be observed among SSRIs, concerning, in particular, serum half-lives and plasma protein-binding percentage.

SSRIs are well absorbed through the small intestine after oral administration, and they reach the peak concentration in 1 to 8 hours.

They are metabolized by the hepatic cytochrome P450 (fluoxetine and paroxetine mainly by CYP2D6; fluvoxamine, fluoxetine, and sertraline by CYP3A4, fluvoxamine by CYP1A2) and undergo the first-pass metabolism. Paroxetine and citalopram are also partly metabolized by the kidneys.

The half-life of SSRIs is highly variable between molecules: from a few hours of fluvoxamine to several days (through active metabolites) of fluoxetine (see table 1).

Pay attention that CYP2D6 is also used to metabolize *dicoumarolic compounds***,** so you should never give Fluoxetine/Paroxetine to a patient taking Coumadin, or you may increase the risk of hemorrhages. Sertraline or citalopram instead should be given to these patients.

The administration of SSRIs with food doesn't change their absorption and could minimize the incidence of gastrointestinal adverse effects.

SSRIs are widely distributed throughout the body and, even though they can cross the placenta, most of them is considered safe during pregnancy.

Table 1. Pharmacokinetics properties of SSRIs

Drug	**Time to Peak Plasma Concentration**	**Half-Life**	**Half-Life Metabolite**	**Time to Steady State (days)**	**Plasma Protein Binding (%)**
Citalopram	4 hours	35 hours	3 hours	7	80
Escitalopram	5 hours	27-32 hours		7	56
Fluoxetine	6-8 hours	4-6 days	4-16 days	28-35	95
Fluvoxamine	3-8 hours	15 hours		5-7	80
Paroxetine	5-6 hours	21 hours		5-10	95
Sertraline	4.5-8.5 hours	26 hours	62-104 hours	7	95

Pharmacodynamics

SSRIs, by the inhibition of the serotonin transporter SERT located on the pre-synaptic cell, block the reuptake of serotonin (5-HT1A, 5-HT2C, 5-HT3C), increasing the level of neurotransmitter available in the synaptic cleft. They are called selective because they exert their function on serotonin with very little effect on other neurotransmitters: dopamine and norepinephrine.

Every SSRI has a similar pharmacologic profile, but slight differences explain their distinct clinical use, side effects, and drug interactions.

Among SSRIs is exhibited very different selectivity for the serotonin transporter, but the clinical efficacy appears to be not directly proportional to the selectivity.

Genetics of SSRIs

The serotonin transporter (SERT) is encoded on chromosome 17q11 which has two possible polymorphisms in the promoter region of the gene leading to two allelic variants (long "l" and short "s"). The long allele is associated with a threefold augmented transcription of the SERT gene compared to the short variant. Consequently, subjects with 1/l genotype have a better response to SSRIs than subjects with l/s genotype, which has a better response than s / s genotype.

Therapeutic indications and clinical use

SSRIs are the first-line treatment for several mental health disorders due to their effectiveness, few side effects, ease of dosing, and low toxicity in overdose.

They are greatly preferred over the other classes of antidepressants in children or adolescents, and they are the first choice for late-onset depression, due to their superior tolerability, minimal anticholinergic effects, and comparatively more benign safety profile.

Clinical indications:

- Major Depressive Disorder
- Obsessive-Compulsive Disorder (first-line treatment: fluvoxamine)
- Generalized Anxiety Disorder
- Panic Disorder (first-line treatment: paroxetine)
- Social anxiety disorder
- Premenstrual Dysphoric Disorder
- Post-Traumatic Stress Disorder (first line: paroxetine)

- Bulimia (first line: fluoxetine)
- Premature ejaculation (paroxetine and sertraline)

Other off-label uses include but are not limited to: Binge eating disorder, Body dysmorphic disorder, fibromyalgia, premature ejaculation, paraphilias, autism, Raynaud phenomenon, and vasomotor symptoms associated with menopause.

Fluoxetine

A starting dose of 10 mg per day is usually preferred to avoid early side effects, especially in patients with concomitant Anxiety or Panic Disorder.

Dosages between 20 to 60 mg per day are commonly required as treatment of depression. Higher dosages of 60 to 80 mg per day may be necessary for the treatment of OCD.

Fluoxetine is preferably administered in the morning and should be taken with food to avoid, respectively, the risk of insomnia or gastrointestinal side effects.

Fluoxetine's most common early side effects are anxiety, agitation, and insomnia; those effects are usually temporary and may improve with a dose reduction or combination with benzodiazepines or beta-adrenergic blockers.

Sertraline

It is recommended a starting dose of 25 mg per day in order to avoid early side effects (anxiety, nervousness, and restlessness), especially in patients with Anxiety or Panic Disorder.

The effective dosage is from 50 to 200 mg a day.

It is useful to administer the drug during a meal to avoid gastrointestinal side effects.

The most common side effects of sertraline are nausea, xerostomia, decreased libido, and fatigue.

Paroxetine

The treatment may start at a dosage of 10 mg per day, particularly for elderly patients or patients with Anxiety disorders. The dosage for the treatment is from 20 to 60 mg a day.

Paroxetine is often chosen as the first-line treatment for Depression, Anxiety disorders, Panic disorder, and Post-Traumatic Stress Disorder.

It is usually administrated as a single dose in the evening but can be administered twice a day.

Paroxetine is the molecule with the highest risk of discontinuation syndrome because its plasma concentration rapidly decreases after suspension. As a consequence, in case of discontinuation, the dosage should be gradually decreased.

Paroxetine appears to be often more sedating and constipating than other SSRIs because of its anticholinergic activity.

Fluvoxamine

Fluvoxamine, although also effective as an antidepressant, is FDA approved only as a treatment for OCD.

The range of effectiveness for the treatment of depression in adults is 50-200 mg per day at bedtime (higher dosages can be divided into two daily administrations). Higher dosages (200-300 mg daily) may be necessary for the treatment of OCD.

Fluvoxamine's short half-life may cause a discontinuation syndrome. In case of discontinuation, the dosage should be gradually decreased.

The most common side effects of fluvoxamine are nausea, headache, and diarrhea.

Citalopram

Citalopram is a racemate consisting of a 1:1 mixture of the R(-)- and S(+)-enantiomers; serotonin reuptake inhibitory activity of citalopram is attributable to the S-enantiomer (escitalopram).

The therapeutic range of citalopram is from 20 to a maximum of 40 mg daily. A maximum dosage of 20 mg per day is suggested for the elderly and patients with hepatic impairment. It can be taken once a day, in the morning or evening, with or without food.

Citalopram is associated with the lowest rate of activating side effects such as anxiety, agitation, and insomnia. The most common side effects are nausea (often transient) and diarrhea. It also shows a low potential for drug interactions.

Escitalopram

Escitalopram is the most selective of the SSRIs. It is the active S-(+)-enantiomer of citalopram.

The dosage recommended in clinical practice is 10 mg a day, and no additional benefits were observed with greater dosages.

The most common side effects are similar to citalopram: nausea and diarrhea. It shows a low potential for drug interactions.

Table 2. Dosage of SSRIs

SSRI	Starting (mg)	Maintenance (mg)	High Dosage (mg)
Paroxetine	10	20–60	>60
Fluoxetine	10	20–60	>80
Sertraline	25	50–200	>300
Citalopram	10	20–40	>60
Escitalopram	5	10–30	>30
Fluvoxamine	50	50–100	>300

Side effects

Pharmacotherapy side effects can strongly affect patients' quality of life and, therefore, their compliance to the treatment.

SSRIs demonstrate superiority in terms of safety when compared to older antidepressant medications. Compared to TCAs, SSRIs do not show cardiac toxicity and orthostatic hypotension, since they are not antagonists of α-adrenergic receptors. Moreover, they have low anticholinergic activity, (except for paroxetine) and do not show typical anticholinergic side effects (dry mouth, blurry vision, constipation, drowsiness, sedation).

Nevertheless, numerous side effects can be observed in patients taking SSRIs. The main side effects of SSRIs are listed below.

- *Gastrointestinal and weight-related side effects*. They are the main SSRIs side effects. They include nausea, dyspepsia, diarrhea or constipation, loss or gain of appetite. Usually, nausea and diarrhea are transient and resolve in few weeks. In up to 25% of people, SSRIs can cause a weight gain of 10 pounds or more, with paroxetine being the most associated with weight gain. Fluoxetine usually induces anorexia and loss of weight, that decrease after a peak at about 20 weeks of treatment. To avoid dyspepsia, nausea or vomiting could be useful to take SSRIs with food. SSRIs are contraindicated in patients affected by peptic ulcers and chronic gastritis.
- *Sexual dysfunction*. Inhibited orgasm or decreased libido, unlike many other SSRIs side effects, are not transient, and lasts as long as the drug is taken. Sexual dysfunction is a dose-dependent side effect, so the first-line strategy to improve SSRI-induced sexual dysfunction

is decreasing the dosage of the SSRI; other options are switching or combining to another not-SSRI antidepressant.

- *Headache.* Though SSRIs are used as effective treatment options and prophylaxis for tension-related headache and migraine, SSRI-related headache has been reported in the first weeks of treatment in up to one-fourth of patients, especially with fluoxetine. It usually reduces spontaneously.
- *Anxiety, agitation, nervousness, and restlessness*. They are some of the most frequent early-side effects, especially related to fluoxetine. They usually appear at the beginning of the treatment and reduce spontaneously after a few weeks. To avoid these side effects, it may be useful to gradually increase the dose of the SSRI or to associate an anxiolytic therapy in the first weeks of treatment.
- *Insomnia and sedation.* The treatment with antidepressants is usually related to sleep improvement due to the reduction of depressive or anxiety-related symptoms. However, up to 25% of people on treatment with SSRIs show sleep disturbances, such as insomnia or sleepiness. Fluoxetine is usually related to insomnia; sertraline can cause both insomnia and drowsiness, while citalopram, paroxetine, and fluvoxamine usually induce somnolence. Molecules causing insomnia are preferably administered in the morning, while the ones causing somnolence should be taken at bedtime. SSRI-related insomnia can be treated with hypnotics or switching to another SSRI
- *Extrapyramidal symptoms.* About one patient on ten shows tremor during an SSRI treatment. Other extrapyramidal symptoms are extremely rare. Parkinson's disease symptoms may get worst after taking SSRIs.
- *Bleeding.* Due to serotonin depletion in platelets, SSRIs are rarely related to *easy bruising*.
- *Rash.* In up to 5% of patients taking an SSRI, a skin rash may appear. In case of allergic reactions, the SSRI has to be suspended.
- *Vivid dreams and nightmares.* Some of patients on treatment with SSRIs report vivid dreams and nightmares. This problem is usually solved switching to another molecule of the same class.

Mood switch

Antidepressant monotherapy is related with an increased risk of mania in patients with bipolar disorder. The risk of a mood switch is far reduced by combining a mood stabilizer and choosing low dosages of antidepressant as maintenance therapies.

Suicide risk

It is important to identify patients with suicidal risk and to monitor them during the first weeks of SSRI therapy, because the suicidal risk is higher at the early stages of relieves from depression.

Serotoninergic syndrome

In extremely rare cases SSRIs can induce a serotoninergic syndrome, usually when combined with other antidepressants (especially MAOIs) that inhibit the reuptake of serotonin.

If plasma levels of serotonin rise to a toxic level, an excess of serotonin activity in the central nervous system and peripheral serotonin receptors may produce specific symptoms: headache, agitation, hypomania, mental confusion, hallucinations, sweating, hyperthermia, hypertension, tachycardia, nausea, diarrhea, myoclonus, hyperreflexia, tremor, and coma.
Mild cases usually resolve in a few hours by discontinuing medications causing an increase in serotonin plasma concentrations. In moderate to severe cases, it may be necessary the administration of a serotonin antagonist (e.g., cyproheptadine) and gastrointestinal decontamination with activated charcoal. Benzodiazepines can be useful to control agitation.

Discontinuation syndrome

The abrupt suspension of drugs determining serotonin reuptake inhibition may lead to a discontinuation syndrome. It is characterized by asthenia, anxiety, agitation, gastrointestinal distress, myalgias, flu-like syndrome (without fever).

Longer durations of treatment and the use of molecules with a short half-life (paroxetine and sertraline) are associated with a higher risk of the above syndrome.
This problem can be avoided by gradually reducing the dosages of SSRI before stopping it.

Drug interactions

SSRIs are metabolized in the liver by CYP450, and their administration can slow or block the metabolism of other drugs.

Fluoxetine and paroxetine reduce the analgesic effect of opioids such as codeine or hydrocodone (CYP2D6). Fluoxetine increases the plasmatic level of carbamazepine by slowing its metabolism. Fluoxetine, sertraline, and paroxetine increase the plasma level of tricyclic antidepressants with possible consequent toxicity. Fluvoxamine interacts with the metabolism of drugs such as theophylline, clozapine (CYP1A2), alprazolam, and clonazepam (CYP3A4).

SSRIs interact with other antidepressants because of their common mechanism of action, increasing the risk of serotoninergic syndrome.

All SSRI displace warfarin from plasma proteins causing higher hemorrhage risk in patients treated with warfarin. Sertraline and paroxetine have the highest potential risk.

Exposure to SSRIs may reduce dopamine turnover, leading to a rise in prolactin levels; they shouldn’t be administered with dopamine antagonists.

Citalopram, escitalopram, and sertraline are considered to have fewer pharmacological interactions than the other molecules.

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRI)

The Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) are a class of drugs blocking neuronal uptake transporters for both serotonin and norepinephrine.

This class of drugs includes eight FDA-approved molecules: venlafaxine (approved in 1993), sibutramine (1998) duloxetine (2004), desvenlafaxine (2008), milnacipran (2009), levomilnacipran (2013). The most commonly used SNRIs are venlafaxine and duloxetine (the only two available in Italy and examined in this chapter).

Pharmacokinetics

Venlafaxine is well absorbed by the gastrointestinal tract and reaches peak plasma concentration in less than 3 hours. The degree of binding of venlafaxine to human plasma is only 25 -30%. It has an extensive first-pass metabolism through the liver and, then, it is primarily eliminated by the kidneys; clearance is therefore reduced among patients with cirrhosis and severe renal disease. The half-lives of venlafaxine and its active metabolite (O-desmethylvenlafaxine) are short: respectively 4 and 10 hours.

Duloxetine is well absorbed from the gastrointestinal tract and reaches peak plasma concentration within 6 hours. The degree of binding of duloxetine to human plasma is about 90%. It is primarily eliminated by the kidneys after hepatic oxidation. It has an elimination half-life of 12 hours, and the steady-state is reached within three days of oral dosing.

Pharmacodynamics

SNRIs are monoamine reuptake inhibitors; specifically, they inhibit the reuptake of serotonin and norepinephrine.

Venlafaxine at the lowest therapeutic doses inhibits the reuptake of serotonin, acting as an SSRI; its noradrenergic effects enhance progressively as the dose is increased.

Duloxetine is a more potent norepinephrine reuptake inhibitor than venlafaxine and acts concomitantly on serotonine and norepinephrine receptors at any concentration.

What distinguishes SNRIs from TCAs is selectivity. SNRIs have a relative lack of affinity for other receptors (muscarinic, histaminergic, α- and β-adrenergic receptors), presenting a more favorable tolerability profile than TCAs.

Therapeutic indications and clinical use

Venlafaxine

Venlafaxine in 1993 was marketed in an immediate-release form that has to be taken two-three times per day. In 1997, it was introduced an extended-release form that allows a once-daily administration. The therapeutic dose is between 75 mg and 375 mg per day; the dosage range is the same for GAD as for the treatment of depression.

FDA Indications: Major Depressive Disorder, Generalized Anxiety Disorder, Social Anxiety Disorder, and Panic Disorder.

The half-lives of *venlafaxine* and its active metabolite are short (4-10 hours), to be kept in mind for the *discontinuation syndrome.* If discontinued, venlafaxine should be gradually reduced in 2-

Duloxetine

The therapeutic dose of duloxetine is between 60 mg and 120 mg per day.

FDA Indications: Major Depressive Disorder, Generalized Anxiety Disorder, Diabetic peripheral neuropathy, Fibromyalgia, Musculoskeletal pain Osteoarthritis.

Side effects

SNRIs may have a variety of side effects related to their mechanism of action: some due to their serotonergic activity, others due to the noradrenergic one.

Nausea, dizziness, insomnia or somnolence, headache, hypertension, sexual dysfunction, asthenia, sweating, constipation, and dry mouth are the most common side effects.

Abrupt discontinuation may produce a discontinuation syndrome. To avoid it, when discontinued, venlafaxine should be gradually reduced in 2-4 weeks.

Side effects usually appear in the first weeks of treatment. A gradual increase in dosage or the use of extended-release forms may reduce the incidence of those side effects.

Drug interactions

No clinically significant drug interactions have been documented but SNRIs should be prescribed carefully in association with other drugs metabolized by CYP450 and with any drug that increases serotonin concentrations (especially MAOIs) to avoid the risk of serotonin syndrome.

Table 3. Inhibitory effect of SSRIs and SNRIs on CYP-450 isoenzymes.

SSRI	*1A/2*	*2C9*	*2C19*	*2D6*	*3A4*
Paroxetine	+	+	+	+++	+
Fluoxetine	+	++	+/++	+++	+/++
Sertraline	-	+	-	+/++	+
Citalopram	-	-	-	+	-
Escitalopram	-	-	-	-/+	-
Fluvoxamine	+++	++	+++	+	++
SNRI					
Venlafaxine	-	-	-	+	+
Duloxetine	+	-	-	+	0

TRICYCLICS AND TETRACYCLICS (TCAs)

Clomipramine, Imipramine, and Amitriptyline are the only TCAs available in Italy.

The name tricyclic and tetracyclic derives from the number of rings present in their chemical structure, three-ring (*tri*) or four-ring (*tetra*).

TCAs are classified according to their receptor selectivity:

- the highest inhibition of serotonin (5-HT) reuptake: clomipramine, imipramine;
- the highest inhibition of norepinephrine (NE) reuptake: desipramine, nortriptyline;
- equal inhibition of both 5-HT and NE reuptake: amitriptyline, amoxapine, doxepin.

Pharmacokinetics

TCAs are rapidly and completely absorbed in the small intestine within 2 to 8 hours. Because of their lipid solubility, these compounds concentrate in different tissues having a high volume of distribution. Since they cross the placenta, they are contraindicated during pregnancy. TCAs are extensively bound to plasma proteins (90%). The concomitant administration of acetylsalicylic acid may reduce the plasmatic protein binding of TCAs, increasing their free levels.

They are metabolized in the liver by the cytochrome P450 system (CYP2D6), with an extensive first-pass metabolism through two main metabolic pathways:

- *Demethylation* converts the tertiary amine to a secondary amine. While demethylated amines cause a stronger inhibition of NE reuptake, tertiary amines exert their effect relatively more on the 5-HT reuptake.
- *Hydroxylation* of the ring structure produces active hydroxyl-metabolites.

TCAs half-lives are approximately 24 hours or longer, and, hence, the drugs can be given once a day.

Pharmacodynamics

Cyclic antidepressants act on five different neurotransmitter systems: serotonin reuptake inhibition, noradrenaline reuptake inhibition, α1 adrenergic receptor inhibition, H1 histaminergic receptor blockade, and muscarinic cholinergic receptor blockade. Each molecule differs in its affinity for each of these transporters. Therefore, secondary effects vary considerably among TCAs.

11.1.1.1. Therapeutic indications and clinical use

Clinical indications:

- Depression, second-line treatment
- Obsessive-Compulsive Disorder (OCD), second-line treatment (clomipramine)
- Panic Disorder (imipramine)
- Generalized anxiety disorder (doxepin)
- Chronic pain and Migraine prophylaxis (amitriptyline)

Each clinical indication for TCAs is also an indication for SSRIs, which are usually preferred to TCAs in clinical practice due to their better tolerability profile. However, TCAs are a valid alternative as second-line treatment in non-responder patients or patients who cannot tolerate SSRIs' adverse effects.

Overdosage may lead to symptoms like agitation, delirium, seizures, tendon hyperreflexia, bladder and rectal paralysis, blood pressure, temperature alterations, mydriasis, and changes in the level of consciousness until coma.

Side effects

TCAs may have a variety of side effects related to their multiple mechanisms of action: α1 adrenergic receptor blockade may cause orthostatic hypotension and dizziness; muscarinic receptor blockade and the resulting anticholinergic action may cause dry mouth, blurred vision, urinary retention, constipation, and memory disorders; H1 histaminic receptor blockade may cause sedation and weight gain.

In case of TCA overdose, blockade of sodium channels in the heart and brain may cause cardiac arrhythmias and seizures.

- *Cardiovascular:* orthostatic hypotension, tachycardia, arrhythmia, and conduction delay. Check QTc during dosage increase.
- *Central Nervous System*: seizures – fine rapid tremor, confusion, or delirium.
- *Autonomic Nervous System*: dry mouth, constipation, blurred vision, urinary hesitancy, ocular crises in patients with narrow-angle glaucoma.
- *Other:* Increased appetite and weight gain, increases in liver enzymes, sexual dysfunction, allergic skin rash, blood dyscrasias (very rare).

The use of TCAs is controindicated in patients affected by known cardiopathy (in particular, arrhytmias and conduction disorders), benign prostatic hyperplasia, glaucoma (narrow-angle).

Drug interactions

TCAs are metabolized by the liver and may have significant interactions with drugs metabolized by CYP2D6, such as fluoxetine, sertraline, and paroxetine (SSRIs), phenothiazines (antipsychotics), carbamazepine (anticonvulsant), propafenone, flecainide, and quinidine (antiarrhythmics).

MONOAMINE OXIDASE INHIBITORS (MAOIs)

Monoamine oxidase inhibitors (MAOIs) were the first class of drugs to be approved for the treatment of depression. The antidepressant effect of the first molecule of this class was discovered by chance: *isoniazid* was originally developed as a treatment for tuberculosis.

MAOIs are effective antidepressants, but they are not commonly used in clinical practice because of the related risk of severe hypertension and the need for dietary control. MAOIs are now rarely used as a treatment for non-responder patients.

MAOIs are a class of drugs inhibiting the activity of one or both monoamine oxidase enzymes: monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B). They include a variety of molecules classified according to their level of selectivity for the type A or B isoenzyme (non-selective/selective for MAO-A/selective for MAO-B) and their chemical structure (hydrazine/non-hydrazine).

Table 4. Classification of MAOIs

Non-selective		Selective IMAO-A	Selective IMAO-B
Hydrazine	***Non-Hydrazine***	• *Moclobemide* • *Pirlindole* • *Toloxatone*	• *Rasagiline* • *Selegiline*
• ***Isocarboxazide*** • ***Isoniazide*** • ***Nialamide*** • ***Phenelzine***	• *Tranylcypromine*		

Pharmacodynamics

The monoamine oxidase is an enzyme on the outer membranes of mitochondria present in two different forms: MAO-A is responsible for the deamination of serotonin and catecholamine (norepinephrine, dopamine, melatonin), while MAO B is responsible for the deamination of phenylethylamine and dopamine. MAOIs act by inhibiting the activity of monoamine oxidase thus preventing the breakdown of monoamine neurotransmitters and increasing their availability.

Monoamine oxidase is located in the brain, liver, intestine, and endothelial cells. MAO-A is mostly located in the placenta and cholinergic neurons, while MAO-B is mostly located in platelets and serotoninergic neurons.

When ingested orally, MAOIs inhibit the catabolism of dietary tyramine, normally metabolized by the hepatic MAOs (primarily MAO-A). High levels of tyramine compete with tyrosine for transportation across the blood-brain barrier entering terminals of the adrenergic nerves and causing a hypertensive crisis through the release of norepinephrine.

People taking MAOIs generally need to avoid foods and beverages containing tyramine: e.g., red wine, beer, cheese, soy sauce, and salami.

Therapeutic indications and clinical use

MAOIs are used to treat atypical depression, anxiety, panic and phobias, bulimia, and PTSD.

Because of potentially lethal dietary and drug interactions, IMAOs are nowadays reserved to treatment-resistant conditions as a last-line treatment.

Side effects

They show many side effects related to their mechanism of action. The most common side effects are cardiovascular effects like dizziness, orthostatic hypotension, and peripheral edema; central nervous system effects as sleep disturbance, sedation, mood switching; general side effects as weight gain and sexual dysfunction. Rarer and more dangerous side effects are hypertensive crisis and serotonin syndrome.

Drug interactions

MAOIs may have interactions with every drug acting on serotonin, norepinephrine, and dopamine: reuptake inhibitors (e. g. SSRIs, SNRIs, TCAs), releasers (e. g. amphetamine, ephedrine), and precursors (e.g. L-dopa, phenylalanine, tryptophan, tyrosine). They also may interfere with drugs metabolized by monoamine oxidase (e. g. phenylephrine).

When switching from an irreversible MAOI to a different antidepressant, a *minimum washout of 2* weeks is required to allow complete recovery of MAO activity.

OTHER ANTIDEPRESSANTS

Vortioxetine

Vortioxetine is a novel antidepressant with multiple pharmacological activities, approved by the Food and Drug Administration (FDA) in 2013 for the treatment of major depressive disorder in adults. In Italy, vortioxetine is available from May 2016.

Vortioxetine has a complex mechanism of action that includes the inhibition of serotonin reuptake through the inhibition of SERT. Moreover, it exerts a direct action at multiple 5-HT receptor subtypes: it acts as an agonist at 5-HT1A receptors, as a partial agonist at 5-HT1B receptors, and as an antagonist at 5-HT3, 5-HT1D, and 5- HT7 receptors.

Some studies have shown a positive effect on cognitive functions in elderly depression.

Nausea, constipation, and vomiting are the most common, dose-related side effects. No significant effect on body weight has been reported.

Bupropion

Bupropion is a mild dopamine and norepinephrine reuptake inhibitor and acts as an antagonist at the nicotinic acetylcholine receptors.

Bupropion is indicated for the treatment of depressive disorders (often used as augmentation therapy of other antidepressants) and smoking cessation.

It is rapidly absorbed by the gastrointestinal tract and then metabolized in the liver by CYP450. It has a half-life of 20 hours and an 80-90% of protein binding percentage.
Bupropion side effects are nausea, dry mouth, excessive sweating, tinnitus, rash, insomnia, anxiety, agitation, tremor, seizure. Sexual impairment has not been observed during treatment with bupropion.

Mirtazapine

Mirtazapine is an antidepressant with a substantial anxiolytic and sedative effect.
Clinical indications of mirtazapine include major depressive disorders (often use as augmentation of other antidepressants), insomnia, and anxiety.
Mirtazapine increases the release of serotonin and norepinephrine by exerting antagonist effects on the central presynaptic alpha-2-adrenergic receptors. It also acts as a strong antagonist of histamine H1 receptors, with marked sedative and appetite-enhancing effects.
Mirtazapine is rapidly absorbed by the gastrointestinal tract, with a hepatic metabolism by CYP450. It has a half-life of 30 hours and a steady state reached after six days of therapy. The dose range is between 15 and 60 mg per day.
The main side effects are sedation (somnolence occurs in more than 50% of patients), dry mouth, increased appetite, and weight gain.

Trazodone

Trazodone is an antidepressant characterized by high sedative qualities.
It was approved by FDA in 1981 for the treatment of major depressive disorders.
Clinical indications of trazodone include depressive disorders, insomnia, and anxiety.
The strong sedative properties, even at a lower dosage, limit its clinical use. On the other hand, the sedative proprieties of trazodone make it beneficial in patients with insomnia.
Trazodone potently antagonizes serotonin 5-HT2A and 5-HT2C receptors, while it just weakly inhibits serotonin reuptake. It has no anticholinergic effects.
Trazodone is rapidly absorbed by the gastrointestinal tract, is metabolized in the liver by CYP450, and is eliminated by kidneys. It has a half-life of 3 hours, and the steady-state is reached after 36 hours, with a 90% protein binding percentage. The dosage varies between 50 and 300 mg per day.
The side effects are related to its antagonism at peripheral α-adrenergic receptors: orthostatic hypotension, dizziness, dry mouth, and priapism.

11.2. ANXIOLYTICS AND SEDATIVES

Introduction

Anxiolytics are a class of drugs used to treat patients with panic disorder, generalized anxiety, and various other conditions. Sedatives (hypnotics) are a class of medications used in a variety of situations, from the treatment of insomnia to the management of epilepsy. Both classes of medications have a wide range of uses and are effective when used in the correct dosage and under the guidance of trained medical professionals. However, their use is burdened by the risk of abuse, which can lead to adverse and potentially fatal consequences.

In this subchapter, we will discuss barbiturates, benzodiazepines, "z-drugs" and antihistamines.

BARBITURATES

Barbiturates were introduced at the beginning of the 20th century as sedative drugs. Due to their narrow therapeutic window and high susceptibility to addiction, they have been gradually replaced by other sedative agents such as benzodiazepines, Z-drugs, and antihistamines. Nowadays, barbiturates are mostly used as anesthetics or anticonvulsants.

Pharmacokinetics

When administered orally, barbiturates are rapidly and completely absorbed by the small bowel, with a latency of action of 10 minutes to an hour. Barbiturates are metabolized in the liver by CYP450, have different plasma protein binding percentages, and cross the placenta.

Pharmacodynamics

Barbiturates exert their action by binding the γ-aminobutyric acid (GABA) receptor and increasing its duration of opening. On the contrary, benzodiazepines only increase the GABA receptor's frequency of opening, resulting in better safety and tolerability. See the paragraph about benzodiazepines for a focus on GABA receptors.

Therapeutic indications and clinical use

Nowadays, barbiturates are only used as anesthetic agents (e.g., for electroconvulsive therapy) and anticonvulsants (in particular phenobarbital).

Side effects

Barbiturates have a strong depressive effect on all the excitatory cells. Moreover, they have a very narrow therapeutic range, and they are associated with a high risk of dangerous overdoses. The symptoms of an acute overdose include motor and speech impairment, respiratory depression with tachycardia, hypotension, hypothermia, oliguria. They can also cause a cardiorespiratory collapse because of a depression in brainstem activity.

BENZODIAZEPINES

Benzodiazepines are a class of drugs widely used in clinical practice worldwide for their anxiolytic, hypnotic, sedative, myorelaxant and anticonvulsant effects. Since their introduction in the early 60s, they have largely replaced older drugs (such as barbiturates) used for the treatment of anxiety and insomnia, thanks to their highly safe profile and tolerability.

Pharmacokinetics

Benzodiazepines are completely absorbed after oral administration and reach peak serum levels in 30 minutes to 2 hours. Intramuscular absorption is slower than the oral one, while the onset of action is very rapid with intravenous administration. Benzodiazepines are lipid-soluble with a binding to plasma proteins from 70 to 99%. As such, they are distributed widely in adipose tissue. They undergo hepatic metabolism, and most of them are oxidized first by cytochrome P450; these metabolites may then be hydroxylated to another active metabolite. Some benzodiazepines (e.g., lorazepam) are conjugated directly by glucuronidation, and, therefore, have a faster metabolism.

The combination of features as lipid solubility, potency, and elimination half-life predicts the onset and duration of action as well as the appropriate frequency of drug administration. Benzodiazepines with high lipophilicity and potency and a short half-life have rapid onset but a brief duration of action, thus causing a stronger withdrawal effect and stronger cravings, whereas agents with a longer half-life have a much more gradual decrease in plasma levels with a lower risk of withdrawal symptoms such as anxiety, excessive arousal, and even seizures.

Pharmacokinetic properties of benzodiazepines substantially affect their clinical use: for example, the rapid onset of action could be very important in the management of a panic attack; the half-life and duration of action are important characteristics in the treatment of insomnia, shorter half-lives are better to treat initial or middle insomnia, while longer half-lives are usually chosen for early morning awakening insomnia. Half-life is also one of the main determinants of the addictiveness of each agent: a short half-life is usually linked to a higher risk of dependence.

Table 5. Classification of benzodiazepines by elimination rates

Classification of benzodiazepines by elimination rates		
Rapid (t ½ < 6 hours)	Intermediate (t ½ 6-20 hours)	Slow (t ½ > 20 hours)
Midazolam	Alprazolam	Clonazepam
Triazolam	Lorazepam	Diazepam
Brotizolam	Temazepam	Chlordiazepoxide
Medazepam	Bromazepam	Alazepam
	Estazolam	Clobazam
	Etizolam	Clorazepam
	Flunitrazepam	Clorazepate
	Lormetazepam	Flurazepam
	Nitrazepam	Ketazolam
	Oxazepam	Nordazepam
	Pinazepam	Prazepam
		Quazepam

Pharmacodynamics

The primary target of benzodiazepines is the GABA-benzodiazepine receptor complex. GABA is the most important inhibitory neurotransmitter in the Central Nervous System (CNS), and its receptor is a chloride channel that opens after the binding with the neurotransmitter, allowing the chloride ions to enter and hyperpolarize the neuron.

The GABA receptor complex is tetrameric, with one α, two β, and one γ subunit. All the molecules that are able to interact with the GABA receptor are subunit-specific.

The benzodiazepine receptor is contiguous to the GABA receptor and is located at the interface between α and γ subunits. Occupancy of this receptor does not affect the chloride ion channel directly but changes the conformation of the receptor, increasing its affinity for GABA. This means that GABA is still needed to activate the neuron, and benzodiazepines only exert their action at sites where a signal mediated by GABA is physiologically present. Barbiturates, on the other hand, facilitate GABA transmission by acting on the sites directly associated with the chloride ion channel, and they hold it open continuously for long periods of time. This is why respiratory failure is one of the worst

fatal effects of barbiturates (as the brainstem is prevented from working properly), while benzodiazepines have optimal tolerability and safety profile.

At high doses, all benzodiazepines mediate four actions: myorelaxant, anxiolytic, hypnotic/sedative, and anticonvulsant; however, at the usual therapeutic dosage, each agent shows an affinity for a certain receptor subtype or a certain subunit, resulting in a different predominant effect, and determining its therapeutic indication and its main clinical use.

Three major subtypes of GABA receptors have been described: two of them are defined central benzodiazepine receptors (CBR) and one is called peripheral benzodiazepine receptor (PBR).

- Ω-1 receptors contain the α1 subunit and are located throughout the CNS. These receptors are responsible for the sedative, hypnotic and antianxiety effects of benzodiazepines.
- Ω-2 receptors, containing α2, α3, or α5 subunits, are located in the cortex, hippocampus, striatum, spinal cord, and on pyramidal neurons. They mediate anxiolysis, muscle relaxation, sedation, and psychomotor impairment and, partly, the anticonvulsant effect.
- Ω-3 receptors (PBRs) are found on glial and other brain cells as well as throughout the body. These receptors, which bind benzodiazepines and the endogenous inverse agonist, are mainly located in the outer mitochondrial membrane and may contribute to tolerance and withdrawal.

Therapeutic indications and clinical use

Benzodiazepines are FDA approved for the treatment of Generalized Anxiety Disorder, Panic Disorder, Post-Traumatic Stress Disorder, Social Anxiety, insomnia, catatonia, acute agitation, delirium, seizure, alcohol withdrawal and addiction, neuroleptic side effects, anesthesia and conscious sedation, spasticity.

Insomnia

Benzodiazepines are widely used to treat insomnia: they increase the quality and length of sleep and reduce sleep latency and REM phases. However, benzodiazepines, in general, should always be used for a predetermined and specific duration, that should be as short as possible. They should be not used for more than 7-10 days without further investigations on the patient's sleep disturbance, because tolerance to the hypnotic effect and dependence develop after few weeks.

Initial insomnia and sporadic nocturnal awakenings should be treated with a short life (such as triazolam) or mid-life benzodiazepine (such as lormetazepam, alprazolam, or lorazepam). On the contrary, early morning awakening insomnia should be treated with longer-life benzodiazepines (such as flurazepam or delorazepam).

Anxiety and depression

Benzodiazepines are the first-choice agents for short-term treatment of anxiety symptoms and acute treatment of panic attacks. Their rapid onset of action, their effectiveness in reducing anxiety symptoms, and their tolerability and safety make them particularly useful for the acute management of these conditions. However, benzodiazepines should be used only as a symptomatic short-term treatment because of the risk of addiction and withdrawal. Both in anxiety disorders and depression benzodiazepines are widely used in combination with antidepressants during the first weeks of treatment, as they are very effective in reducing the anxiety symptoms that often appear as early side effects of the antidepressant therapy. They are then usually reduced in few weeks, once the antidepressant starts to be effective.

Acute agitation

Acute agitation may occur in a variety of medical and psychiatric conditions. On these occasions, it is often necessary to rapidly calm the patient to prevent dangerous behaviors for the patient himself and others, as well as to properly recognize and treat the underlying condition. Intramuscular benzodiazepines, alone or combined with an antipsychotic, are a widely used and effective strategy to achieve this goal. Lorazepam is the most used agent, among benzodiazepines, for acute agitation treatment.

Alcohol withdrawal

Alcohol causes symptoms of toxicity by a direct effect on the benzodiazepine receptor. That is why benzodiazepines may be useful in the management of alcohol addiction in order to avoid alcohol withdrawal symptoms such as tremors and dizziness, difficulty in sleeping, nausea and vomiting, irritability, headaches, pain, anxiety, and panic. The goal of the treatment is to minimize withdrawal symptoms and then lead to a controlled tapering of the drug. Diazepam, chlordiazepoxide, and lorazepam are often used to control alcohol withdrawal. Benzodiazepines, in general, can be used with different strategies. A fixed dosage can be administered concomitantly with the discontinuation of alcohol and then slowly tapered, but, in a hospital setting, benzodiazepine dosage may also be patient-tailored, depending on the symptoms and the clinical situation.

Seizures

Benzodiazepines exert a general action of reduction of neuron firing, by eliciting the action of the most important inhibitor neurotransmitter, GABA. That makes them effective for the treatment of seizures. In chronic conditions, benzodiazepines are used as adjunctive therapy to anticonvulsant agents, and clonazepam is the most frequently used agent because of its long duration of action. Benzodiazepines are also useful for the management of acute seizures: in particular, rectal diazepam

has a fast onset of action and is an accessible way of administration also during a convulsive seizure and in out-of-hospital settings. Intravenous diazepam, lorazepam, and midazolam are often and effectively used in the treatment of the status epilepticus.

Neuroleptic side effects

Benzodiazepines can be used to treat neuroleptic side effects: akathisia and acute dystonia in particular. Akathisia is a common and very annoying side effect of antipsychotic agents, characterized by restlessness and mental unease. Benzodiazepines may be effective in reducing or solving this condition, resulting in relief for the patient and making the treatment more tolerable.

Table 6. Parmacokinetics properties of benzodiazepines.

Agent	Dose eq. approx.*	Half-life** [hours]	Duration**	Usual dosage [mg die]
Alprazolam	0.25	12	Short	0.5-6
Bromazepam	1.5	10-20	Medium	3-18
Brotizolam	0.25	3-6	Short	0.25-0.50
Clobazam	5	30	Long	10-30
Clonazepam	0.5	34	Long	0.5-10
Clorazepam	1	80	Long	1-6
Clorazepate	7.5	100	Long	7.5-60
Chlordiazepoxide	10	100	Long	15-100
Clotiazepam	2.5	-	-	5-30
Diazepam	5	100	Long	2-60
Estazolam	0.33	17	Short	1-2
Etizolam	-	15	Medium	0.50-2
Flunitrazepam	-	15-30	Medium	0.50-2
Flurazepam	5	100	Long	15-30
Ketazolam	5	100	Long	5-30
Lorazepam	1	15	Short	2-6
Lormetazepam	0.5	10-15	Medium	1-2
Nitrazepam	1.5	18-30	Medium	2.5-5
Oxazepam	15	8	Short	15-60
Prazepam	10	100	Long	20-40
Temazepam	5	11	Short	20-40
Triazolam	0.1	2	Short	0.125-0.25

*High potency < 1; medium 1-10; high potency > 10

**Short acting: half-life < 25 hours

Side effects

The therapeutic action of benzodiazepines may also result in side effects: in particular, their sedative effect often causes daytime drowsiness and decreased concentration, which may interfere with driving and global functioning. Other side effects of benzodiazepines are mild memory impairment, anterograde amnesia, psychomotor impairment with increased risk of falling, agitation, and depression. They also often cause a worsening of Obstructive Sleep Apnea Syndrome (OSAS).

Dependence and withdrawal

Discontinuation of treatment with benzodiazepines may lead to different clinical scenarios:

1. Relapse: the return of the same symptoms treated with benzodiazepines.
2. Rebound: the intensification of symptoms treated with benzodiazepines. It starts within a few days of drug discontinuation and lasts from days to weeks, according to the duration of the treatment.
3. Withdrawal: the onset of new autonomic symptoms that are not components of the original disorder but a consequence of tolerance and dependence. It begins within hours to days of discontinuation, and it lasts for days to weeks, depending on the drug's half-life: from few days for shorter-acting benzodiazepines to two weeks for longer-acting ones. The symptoms of the withdrawal syndrome include anxiety, sleep disturbances, photophobia, phonophobia, mild hypertension and tachycardia, gastrointestinal distress, sweating, tremor, headache, seizures.

In order to avoid addiction and discontinuation syndrome, benzodiazepines should be used at the lowest effective dose and for the shorter possible period. In particular, short half-life agents and drop formulations appear to be the most addictive and are more likely to cause withdrawal syndromes when discontinued.

Discontinuation of treatment with benzodiazepines needs to be considered if: symptom relief is achieved, duration of treatment is longer than one month, the patient is taking an excessive dosage, the patient is over 65 years old, the patient is taking concomitant CNS sedatives, the patient is affected by cognitive disorders, in case of traumatic brain injury and the patient has a history of substance or alcohol abuse, or the abuse is still active.

Different strategies should be applied to properly discontinue treatment with benzodiazepines: an individualized and gradual tapering scheme, patient education, a possible concomitant cognitive-behavioral approach, and proper management of the withdrawal symptoms.

Tapering can be started with the same medication or after a switch to an equivalent dose of a longer half-life agent, and it should consist of a 25% reduction every two weeks, followed by a slower reduction of 12.5% every two weeks. Adjunctive medications may be useful to reduce the negative

effects of benzodiazepine discontinuation, such as antidepressants or anticonvulsants (e.g., gabapentin, pregabalin).

Benzodiazepine overdose is usually not life-threatening: the main symptoms include CNS depression, impaired balance, ataxia, and slurred speech. Rarely, and usually when benzodiazepines are combined with alcohol or other drugs, more severe symptoms may appear, including coma and respiratory depression.

Flumazenil is indicated for the treatment of benzodiazepine overdose. It is a benzodiazepine receptor antagonist: acting on the GABAA receptor, it counteracts the action of benzodiazepines. It has a 1-hour half-life and is administered intravenously at a dosage of 0.2-0.3 mg over 15 seconds, followed by repeatable 0.1 mg every 60 seconds, until a maximum dose of 1-2 mg.

Drug interactions

Antacids may reduce the gastrointestinal absorption of benzodiazepines. Some interactions are possible with drugs or substances metabolized by CYP450: inhibitors like erythromycin, ketoconazole, cimetidine, estrogen, disulfiram, verapamil, nefazodone, and grapefruit juice, increase benzodiazepine plasma levels, while carbamazepine and St. John's Wort, which induce the enzyme, lower benzodiazepine plasma levels.

Side effects of benzodiazepines, as well as the severity of an overdose (e.g. in a suicide attempt), are significantly increased by concomitant *intake of alcohol* because of their common receptor target and because of the hepatic metabolism of alcohol, which interferes with the metabolism of benzodiazepines increasing their blood levels.

Z-DRUGS: ZOLPIDEM, ZALEPLON AND ZOPICLONE

Zolpidem, zaleplon, and zopiclone are usually called *z-drugs* because of their names starting with the letter “Z”. They are sedative drugs that act selectively on the Ω-1 benzodiazepine receptor, resulting in better tolerability and fewer side effects compared to benzodiazepines.

Pharmacokinetics

Z-drugs are rapidly absorbed after oral administration. They have different half-lives: from 1 and 2 hours respectively for zolpidem and zaleplon to 5-7 hours for zopiclone. Zolpidem has a high bioavailability (about 70%), while zaleplon and zopiclone have a lower bioavailability (about 30%) due to extensive first-pass metabolism. They are oxidized to inactivate metabolites.

Pharmacodynamics

Z-drugs are selective for the benzodiazepine-1 receptor, without relevant effects on other benzodiazepine receptor subtypes at clinical dosages. Lack of effect on benzodiazepine-3 receptor may determine a lower incidence of withdrawal and rebound symptoms. *Z-drugs' activity* can be blocked by the benzodiazepine receptor's antagonist flumazenil.

Therapeutic indications and clinical use

Z-drugs are used for the treatment of insomnia; they have a hypnotic and anxiolytic action, without the muscle relaxant and anticonvulsant effects typical of benzodiazepine. Z-drugs are effective hypnotics, but they do not help the regulation of the sleep-wake cycle. Zolpidem seems to improve total sleep time similarly to benzodiazepines, but without modifying sleep structure. It causes no daytime sleepiness or lowering in mental concentration. Zaleplon is often chosen for nighttime awakenings due to its short duration.

Table 7. Dosage of Z-drugs

Drug	**Initial dose**	**Maximum dose**
Zolpidem	5 mg	20 mg
Zaleplon	5 mg	10 mg
Zopiclone	1 mg	3 mg

Side effects

Zolpidem, zopiclone and, zaleplon are generally better tolerated than benzodiazepines as regards to daily somnolence, dullness, and lack of concentration, but they may have side effects as sedation, anterograde amnesia and higher risk of falling, in particular in the elderly. Tolerance and rebound insomnia are less likely to happen in patients in therapy with z drugs than benzodiazepines, but they can occur after chronic use.

ANTIHISTAMINES

Pharmacokinetics

Antihistamines have good oral absorption and a plasma protein binding between 50% and 98%, with a wide distribution in the body and the CNS. They are metabolized in the liver by CYP2D6 and CYP3A4. Their half-life varies between 2 and 27 hours, and they reach a peak in blood levels in 1-3 hours.

Pharmacodynamics

Antihistamines are antagonists of histamine receptors. Agents blocking the action of H2 histamine receptors are very selective and are used as antacids. Molecules acting on the H1 receptor, on the other hand, are mainly used for the treatment of allergic conditions but also have a CNS sedative action.

Therapeutic indications and clinical use

Antihistamines are mostly used for the treatment of non-psychiatric conditions, in particular allergic symptoms. However, their sedative effect on the CNS may also be useful for the treatment of insomnia, while their anticholinergic effect can be beneficial for neuroleptic side effects such as Parkinsonism, acute dystonia, and akathisia.

As sedative agents, antihistamines are not more effective than benzodiazepines, and their tolerability and safety have been less studied; therefore, benzodiazepines are usually preferred. Antihistamines are not used as long-term anxiolytic therapy.

Side effects

Antihistamines' use is associated with side effects, such as dizziness, daily sleepiness, and hypotension. Impairment in attention and concentration can also appear and may be particularly dangerous for driving or specific jobs. Other side effects include symptoms related to their mild anticholinergic activity, like blurred vision, urinary retention, constipation, dry mouth. The elderly are more likely to show side effects, including a psychomotor impairment, that may lead to an increased risk of falling.

Antihistamines should be avoided during breastfeeding, since they are excreted with the milk, and in pregnancy because of potential damage to the fetus.

Drug interactions

Because of their sedative effects, antihistamines should be administered very carefully in combination with other CNS depressants, including benzodiazepines, dopamine receptor antagonists, tricyclic antidepressants, and alcohol.

11.3. MOOD STABILIZERS

Introduction

Mood stabilizers are medications used to treat bipolar disorder, schizoaffective disorder, and borderline personality disorder.

These drugs help to maintain euthymia, reducing mood swings and preventing manic and depressive episodes in bipolar and schizoaffective disorder. They are also used to supplement other medications, such as antipsychotics or antidepressants, in the treatment of acute mania or depression.

Mood stabilizers are also effective in reducing borderline personality disorder symptoms, including emotion dysregulation, mood lability, and impulsivity. Medications commonly classified as mood stabilizers include salts, anticonvulsants, and antipsychotics. Antipsychotics are discussed in their specific subchapter.

LITHIUM

Lithium is the most prescribed mood stabilizer worldwide. Lithium is an anion, and it follows hydrogen and helium on the periodic table, making it the third simplest chemical element. How such a simple element can have such a great pharmacological effect is still not completely clear, although its effectiveness was first demonstrated in the 50s and it was approved by FDA for the treatment of mania in 1974.

Pharmacokinetics

Lithium is rapidly and completely absorbed when administered orally, with serum concentrations peaking in 1 to 1.5 hours. It has no clinically relevant protein-binding properties and no metabolites.

It is excreted almost exclusively by the kidneys, with small amounts are also eliminated through sweat and feces. A significant portion of filtered lithium is reabsorbed (mainly in the proximal tubules): this implies that other drugs acting at the level of proximal tubules may interfere with lithium reabsorption (e.g., thiazides). The elimination half-life of lithium is about 18 to 24 hours, although it is considerably longer in the elderly because of the age-related decrease in the glomerular filtration rate. Therefore, older subjects usually require lower than usual dosages to achieve therapeutic serum concentration and reach a steady state over longer periods of time than usual.

Lithium is broadly distributed throughout the body, with different extent into tissues: thyroid and renal concentrations are greater than serum levels, differently from red blood cell and brain concentrations. Lithium enters and leaves the CNS slowly; for this reason, acute intoxication with

high plasma levels are sometimes well-tolerated, and clinical manifestations of chronic intoxications often persist for long periods after plasma levels have decreased.

It is possible to dose both the lithium serum concentration and the concentration of lithium inside red blood cells (RBC). This is important because lithium persists inside red blood cells for about 7 days, while the serum concentration of lithium 48 hours after the last administration is almost zero. RBC lithium concentration is a more reliable indicator of therapy adherence and is useful for the diagnosis and prognostic evaluation of lithium poisoning because toxic symptoms do not always correlate with plasma concentrations.

Pharmacodynamics

Although lithium is widely considered the first choice among mood stabilizers, it is not completely clear how it works. What does seem clear is that amount of lithium required for its clinical effect is much greater than the traces normally present in the body, thus the cause of bipolar disorder is not a lithium deficiency.

There are several targets for its mechanism of action: from the microscopic intracellular signaling to the macroscopic brain structure. Lithium can modify nuclear transcription factors and influence gene expression: it generates *posttranslational modifications of G proteins;* it inhibits proteins such as PKC, MARCKS, GSK-3, IPPase, and IMPase. Lithium modulates dopamine, glutamate, and GABA neurotransmission. Some findings suggest that lithium's stabilizing effect might be related to the modulation of dopamine (associated with depression), NMDA or AMPA receptors for glutamate (antimanic effect), and GABA neurotransmission. Acting on BDNF and BCL2, the chronic use of lithium is probably associated with neuroprotection and neuroproliferation. Changes in the brain structure are associated with chronic use of lithium; in literature changes in the anterior cingulate cortex, the ventral prefrontal cortex, the hippocampus, and the amygdala have been reported.

Ion transport theory

Neural transmembrane potential differences are maintained by sodium pumps and perturbations of this system seem to be present in patients with bipolar disorder. Some studies associated the alteration in sodium pump activity causing neurotransmitter aberrations to mood oscillations. Lithium is thought to stabilize membrane function.

Lithium and GSK3

Lithium inhibits glycogen-synthase kinase3 (Gsk3) and inositol monophosphatase (IMPase). GSK3 is a protein kinase involved in many signal transduction cascades influencing protein phosphorylation, microtubular dynamics, cell proliferation and development, and neuronal apoptosis. Recent studies have shown that glycogen synthase kinase 3-β (GSK3-β) is involved in the control of cell behavior and in the mechanism of action of lithium and serotonergic antidepressants, and in humans a certain promoter variant was associated with reduced activity and better antidepressant response.

Gene-gene interactions between components of the monoaminergic signal transduction pathways and of plasticity related pathways can shape the individual antidepressant response. In particular, GSK3-β influences synaptic plasticity and cell resilience, counteracting the detrimental influence of the short form of the serotonin promoter on antidepressant response.
These new findings highlight the important role of GSK3 as a mediator of the action of lithium

Therapeutic indications and clinical use

Lithium is FDA approved for the acute treatment for manic episodes and as maintenance therapy in bipolar disorder. Off-label uses of lithium are the prevention of depressive episodes in Major Depressive Disorder and the control of emotion dysregulation, mood lability, and impulsivity symptoms in borderline personality disorder.

Long-term treatment with lithium has proven to be an effective way to reduce frequency, severity, and duration of mood episodes in patients affected by Bipolar Disorder.

In the acute manic phase, lithium treatment aims at the remission of the episode. At the resolution of the episode, there should follow a continuation (6-9 months) and a maintenance phase (minimum 2 years) to prevent, respectively, relapses and recurrences of the illness.

It's often recommended to start the lithium treatment from the first episode of mania.

The discontinuation of successful lithium treatment, especially if rapid, is associated with a substantial increase of the recurrence risk. After the discontinuation, the reintroduction of lithium therapy often appears to be less protective against mood episodes.

Before starting lithium treatment, it is important to consider the patient's characteristics such as age, comorbidities, and concomitant pharmacotherapies. Some medical evaluations are also necessary: renal and thyroid functions should be routinely tested before beginning treatment. A pregnancy test is recommended for women of childbearing age.

The therapeutical dosage is between 600-1200 mg/day divided into 2 doses approximately 12 hours apart (morning-night).

Lithium serum levels, creatinine, TSH, FT4, electrolytes, and urinalysis should be checked regularly during treatment (every 6-12 months).

Lithium serum level should be checked every 3 months (blood should be collected 12 hours after the last administration); the therapeutic range has been established at 0.5-0.8 mmol/L during active manic phases, and at 0.4-0.6 mmol/L as maintenance treatment.

Table 8. Lithium prescribing and monitoring

<table>
<tr><td colspan="3">LITHIUM PRESCRIBING AND MONITORING</td></tr>
<tr><td>Before treatment</td><td colspan="2">Monitoring</td></tr>
<tr><td rowspan="13">Blood Urea Nitrogen
Creatinine
Urinalysis
Urine volume 24h
Creatinine clearance
TSH
Free and total T4
Free and total T3
Complete Blood Count
Electrolytes
Glycemia
Electrocardiogram
Blood pressure
Pregnancy test (childbearing age)</td><td colspan="2">Minimum recommendations</td></tr>
<tr><td>Lithium serum levels</td><td>6-8 weeks</td></tr>
<tr><td>Creatinine</td><td>6-12 months</td></tr>
<tr><td>TSH</td><td>6 months</td></tr>
<tr><td>fT4</td><td>6 months</td></tr>
<tr><td>Electrolytes</td><td>6-12 months</td></tr>
<tr><td>Urine analysis</td><td>12 months</td></tr>
<tr><td colspan="2">Additional recommendations</td></tr>
<tr><td>Urine volume 24 h</td><td>6-12 months</td></tr>
<tr><td>Creatinine clearance</td><td>6-12 months</td></tr>
<tr><td>Urine osmolarity</td><td>6-12 months</td></tr>
<tr><td>Complete Blood Count</td><td>6-12 months</td></tr>
<tr><td>Electrocardiogram</td><td>6-12 months</td></tr>
<tr><td>Intraerythrocytic lithium</td><td>3 months</td></tr>
</table>

Lithium and neurodegeneration

MRI studies on patients affected by Bipolar Disorder showed a widespread disruption of brain white matter structure.

Long-term administration of lithium appeared to be associated with an increase of axial diffusivity (reflecting integrity of axons and myelin sheaths) in several white matter fiber tracts contributing to the functional integrity of the brain and involving interhemispheric, limbic, and large frontal, parietal, and fronto-occipital connections. This effect of lithium is related to its well-known GSK3 inhibition.
These findings further demonstrate the importance of long-term treatment with lithium in people suffering from Bipolar Disorder, shedding new light on its long-term beneficial effect.

Absolute contraindications: psoriasis, renal dysfunction, myasthenia gravis, acute myocardial infarction, diabetes insipidus, severe electrolyte imbalances.
Relative contraindications: thyroid diseases, chronic heart disease (e.g., hypertension, valvular disease), pregnancy, breast feeding, Parkinson's disease, cerebellar disorders, ulcerative colitis, hypertension treatment.

Side effects

The majority of patients taking lithium experience adverse effects, but less than 20% have more than minor complaints.

Following is a list of the main side effects:

- *Renal:* urinary concentrating defect, polyuria (nephrogenic diabetes insipidus), reduced glomerular filtration rate, nephrotic syndrome (absolute contraindication for administration of lithium).
- *Endocrine:* hypothyroidism.
- *Neurological:* dysphoria, slowed reaction time (rare), tremor (postural, occasional extrapyramidal), peripheral neuropathy, myasthenia gravis-like syndrome.
- *Gastrointestinal:* appetite loss, nausea, vomiting, diarrhea, altered carbohydrate metabolism, weight gain, fluid retention.
- *Dermatological:* acne, hair loss, rash. Psoriasis is an absolute contraindication.

Lithium can interfere with the synthesis of thyroid hormones because of its similarity with iodine. 7-9% of patients in treatment with lithium may thus develop *functional hypothyroidism* without thyroid damage. This condition should be treated with synthetic thyroid hormone levothyroxine; the disruption of effective treatment with lithium is not indicated in these cases.

Drug interactions

Most nonsteroidal anti-inflammatory drugs reduce renal lithium clearance and increase the serum lithium concentration with potentially dangerous consequences. The newer COX-2 inhibitors, such as celecoxib and rofecoxib are no exception.

Thiazide diuretics reduce renal lithium clearance and increase the plasma lithium concentration. Lithium retention may also be caused by potassium-sparing diuretics. Conversely, loop diuretics such as furosemide may increase renal lithium clearance.

Lithium is known to be a potential precipitant of serotonin syndrome in people concurrently on serotoninergic medications, such as antidepressants. Lithium co-treatment is also a risk factor for neuroleptic malignant syndrome in people treated with antipsychotics and other antidopaminergic medications.

Lithium intoxication

Lithium has a narrow therapeutic index, and a higher level of lithium can lead to intoxication. Lithium intoxication leads to neurotoxicity that can, in extreme cases, result in death or permanent neurological damage. Clinical presentation of lithium intoxication includes gastrointestinal manifestations, dysarthria, ataxia, tremor, impaired consciousness, neuromuscular irritability (fasciculations, myoclonus), and seizures.

Lithium toxicity can occur due to excessive intake or decreased excretion. Some factors may decrease its excretion: kidney disease, dehydration, drug interaction, and a low-sodium diet.
The diagnosis is generally based on symptoms and is supported by a high serum (and/or RBC) lithium level.
Treatment of lithium intoxication consists of lithium discontinuation, gastric lavage, hydration, proper fluid, and electrolyte balance.

Lithium and pregnancy

Lithium is probably the most effective treatment for the prevention of mood episodes, even during pregnancy and postpartum. Even if many studies throughout the years have suggested, especially in the first trimester, an increased risk of fetal abnormalities, more recent studies have estimated a lower risk than previously reported. More research is certainly needed to be conclusive.

Lithium could be suspended during pregnancy or after delivery but the higher risks of relapse, especially in the postpartum period, should be carefully considered. When lithium is discontinued, it should be restarted immediately after delivery for relapse prevention.
If lithium is administered during pregnancy, the dose can be reduced, especially in the first trimester, and the lithium blood level should be checked more frequently (up to once a week). Fetal echocardiography between weeks 16 and 20 of gestation may be cosidered due to the potential increased risk of cardiac malformations. Lithium dosage should be decreased or discontinued few days before delivery to reduce the risk of maternal and neonatal toxicity. Due to a high infant/maternal ratio of serum drug concentration, breastfeeding is not recommended. Different mood stabilizers, such as valproate or carbamazepine, have to be avoided during pregnancy. Lithium is, therefore, the first-choice maintenance therapy for pregnant women affected by Bipolar Disorder.

VALPROATE

Valproic acid is an anticonvulsant, first-line treatment of Bipolar Disorder (mania, mixed states, and as maintenance therapy), useful in treating epilepsy, in preventing migraine headaches, and in reducing borderline personality disorder symptoms, such as emotion dysregulation, mood lability, and impulsivity.

Pharmacokinetics

All formulations of valproate are rapidly absorbed, with peak plasma concentrations obtained 3 to 4 hours after oral administration. The plasma half-life of valproate is 10 to 16 hours; however, a shorter half-life is recorded when administered in combination with inductors of cytochrome P450. Valproate is highly protein-bound, primarily to albumin, but only the unbound portion of valproate is considered to be pharmacologically active since it crosses the blood-brain barrier. Higher serum levels than 45 to 50 µg/ml saturate all the binding sites with an increase of unbound valproate. This drug is metabolized primarily through hepatic glucuronidation and mitochondrial β-oxidation. Several valproate metabolites, as 2-propyl-2-pentenoic acid and 2-propyl-3-oxopentanoic acid, have potent anticonvulsant activity.

Pharmacodynamics

The anticonvulsant and mood stabilization mechanisms of action have not been specifically identified and may not necessarily be the same. The anticonvulsant effect is rapid in onset, while the mood-

stabilizing one is slower and requires chronic administration. GABA deficit hypothesis, proposed by Emrich in 1980, suggested that bipolar illness was characterized by a relative deficit of GABA that could be ameliorated with valproate administration. Several hypotheses include enhancement of GABA levels via multiple actions of synthesis, degradation, and modulation of other neurotransmitters, voltage-sensitive Na channels, extra hypothalamic neuropeptides, secondary messenger systems, and neuroprotection. Preclinical studies have shown that valproate enhances GABAergic function in specific regions of the brain by means of a variety of presynaptic or postsynaptic mechanisms: the enhancement of GABA synthesis through the activation of glutamate decarboxylase, the prevention of GABA catabolism through the inhibition of GABA transaminase, the direct release of GABA in response to calcium influx, the reversal of the GABA transporter, or postsynaptic GABAA receptor activation effects.

Therapeutic indications and clinical use

Valproate is currently FDA-approved as treatment for seizures, acute mania, or mixed states, as prevention of recurrent manic and depressive episodes (it has been recommended as a first-line option in many treatment guidelines), and as prevention of migraine headaches. It is also used off-label (for unapproved uses) for other conditions such as borderline personality disorder, impulse-control disorder, and agitated behavior in dementia, because of its effectiveness in reducing emotion dysregulation, mood lability, irritability, aggressiveness, and impulsivity.

It is particularly effective in the treatment of acute mania, also when associated with depressive or dysphoric symptoms (mixed states), with a rapid-cycling course of illness (four or more episodes in a 12-month period), and manic episodes complicated by substance or alcohol abuse. In patients with chronic alcohol abuse associated with hepatic dysfunction, lithium is preferred because it is not metabolized by the liver. Given its current neurological FDA indications, valproate may be particularly useful in bipolar disorders complicated by seizures, electroencephalogram (EEG) abnormalities, head trauma, and migraines.

Side effects

Although valproate treatment is usually well-tolerated and safe, it is associated with serious adverse effects, including hepatic failure, pancreatitis, hyperammonemic encephalopathy in patients with urea cycle disorder, sedation in the elderly, and thrombocytopenia. To avoid these severe reactions, it is important to carry out baseline hepatic function tests before starting valproate treatment. However, serial laboratory monitoring does not necessarily predict severe hepatotoxicity or pancreatitis.

Minor, and more common, adverse reactions include gastrointestinal distress, tremor, sedation, benign hepatic transaminase elevation, leukopenia, thrombocytopenia, hair loss, increased appetite, and weight gain. Most of the common adverse effects are dose-related and may be prevented or minimized by dose reduction or adjunctive pharmacotherapy.

Valproate is contraindicated and should not be taken by pregnancy: it is associated with teratogenicity, with risk of neural tube defects and heart malformations. All non-pregnant women of childbearing age taking valproate products should use effective birth control.

Drug interactions

Valproate is commonly prescribed in combination with other psychotropic agents. The combination with lithium is generally well tolerated and is often more effective than valproate alone. However, a problem may be the additive side-effect burden of the two medications: tremor, cognitive dulling, and dyspepsia. Typical antipsychotics and valproate are often prescribed together, especially in acute mania. Again, increased sedation and an increase in extrapyramidal side effects have been reported. More recently, atypical antipsychotics and valproate have been used together, with increased sedation and weight gain reported as side effects. Valproate has also been used as an adjunctive mood stabilizer and anticonvulsant in patients treated with clozapine. In fact, for patients who have had a seizure related to a high dose of clozapine, valproate is preferred over carbamazepine, burdened by an additional risk of agranulocytosis. The combination is generally well tolerated, except for sedation and weight gain.

In contrast to carbamazepine, the primary pharmacokinetic liability of valproate is related to its plasma protein binding capacity and to the inhibition of other drugs hepatic metabolism. For example, valproate increases the free concentration of diazepam by plasma protein binding site displacement and reduces the serum level of a diazepam metabolite: N-desmethyldiazepam. Close clinical monitoring of this coadministration is therefore indicated to avoid toxicity. Similar observations have been noted with phenobarbital, chlorpromazine, and aspirin. Because valproate has been shown to inhibit the secondary phase of platelet aggregation, close clinical monitoring is indicated when using the drug with other drugs that affect coagulation, such as aspirin and warfarin.

CARBAMAZEPINE

Carbamazepine is an anticonvulsant medication used primarily in the treatment of epilepsy and neuropathic pain. It has been recommended in many treatment guidelines as a second-line agent mood stabilizer in Bipolar Disorder.

Pharmacokinetics

Carbamazepine is absorbed slowly and inhomogeneously through the gastrointestinal tract. It is metabolized in the liver and then excreted by the kidneys, as only 1 percent is eliminated by biliary excretion. Peak plasma levels are achieved 2- 8 hours after a single dose and the molecule is 70-80% bound to plasma protein. The half-life after a single dose range from 18 to 54 hours. However, with long-term intake, the half-life decreases to about 10 to 25 hours due to the autoinduction of hepatic P450 enzymes, which increase the metabolism of carbamazepine itself. The degree of the drug autoinduction is dose-dependent but is generally complete after 3 to 5 weeks of treatment. As a consequence, tolerability improves after several weeks of treatment, and blood levels may be markedly reduced despite the use of the same daily dose.

Pharmacodynamics

The onset of anticonvulsant and antinociceptive effects is rapid and occur approximately after 24 to 48 hours. Antimanic actions of carbamazepine usually begin within the first days of treatment, but often an optimal response in patients is achieved only after several weeks. The anticonvulsant effects of carbamazepine have been mainly associated with blockade of type 2 sodium channels, which, when inactivated, reduce the release of excitatory amino acids such as glutamate and inhibit sustained rapid neuronal firing. Carbamazepine also act as a potent agonist on adenosine A1 receptors, which mediate not only some of its anticonvulsant actions but also its sedative properties.

As well as lithium and valproate, carbamazepine blocks inositol transport at the myoinositol transporter. The antinociceptive effects of the drug have been mainly linked to effects at GABA-B receptors and are specifically inhibited by GABA-B antagonists. Interestingly, chronic (and not acute) administration of lithium, carbamazepine and valproate determine upregulation of GABA-B receptors in the hippocampus. This action may represent a potential convergent mechanism for mood stabilization.

Therapeutic indications and clinical use

FDA-approved indications for carbamazepine use are epilepsy (partial seizures and tonic-clonic seizures), trigeminal neuralgia, manic and mixed episodes of Bipolar I Disorder. Carbamazepine is also widely used in bipolar disorder as long-term prophylaxis: many guidelines suggest carbamazepine as first or second-line drug for mood stabilization. Moreover, it can be used as a substitute or as an adjunct to lithium in partial responders. Carbamazepine is also highly effective in a wide range of aggressive and impulse-control disorders that can occur in patients affected by personality disorders, affective disorders, and schizophrenia.

Even if carbamazepine appears to be approximately as effective as lithium in the prevention of affective episodes, some insights are needed. Lithium appears to be more effective than carbamazepine in preventing manic episodes in patients with Bipolar Disorder Type I with a positive family history of affective disorder and no alteration in thought content or comorbid substance abuse. Conversely, carbamazepine showed better prophylactic efficacy in patients with Bipolar Disorder Type II, Schizoaffective Disorder, dysphoric manic episodes, and substance abuse comorbidity, as well as a negative family history for affective disorder. In some cases, patients may respond to carbamazepine after failing to respond to valproate or vice versa, consistently with the notion that response to the anticonvulsants does not occur as a class effect.

Side effects

Carbamazepine, when used in the treatment of psychiatric conditions, is usually administered at lower dosages than in the treatment for epilepsy. However, a variety of side effects can be observed in patients treated with low doses, too.

- *Hematological:* **t**he most frequent hematological side effect is a clinically not-significant suppression of the white blood cell count due to the inhibition of the colony-stimulating factors. Potentially life-threatening blood dyscrasias such as agranulocytosis or aplastic anemia occur in approximately 1 in 100.000 patients. Patients should be warned that, if signs of potential hematological dysfunction (such as fever, sore throat, rash, petechiae, bruising, or overt bleeding) appear, they should immediately seek medical assistance.
- *Dermatological:* about 10-15 percent of people treated with carbamazepine develop a benign maculopapular rash typically emerging in the first 10 to 30 days after drug initiation. Drug cessation usually leads to the resolution of the rash. In rare instances, carbamazepine can induce a variety of dermatological syndromes, some of which are serious, including exfoliative dermatitis, erythema multiforme, Stevens-Johnson's syndrome, or toxic epidermal necrolysis.

- *Endocrine:* carbamazepine increases the 24-hour excretion of urinary free cortisol and decreases circulating levels of thyroxin (T4) and triiodothyronine (T3), without altering TSH. However, thyroid replacement is rarely required.
- *Renal:* carbamazepine has an agonist-like effect on the vasopressin receptor and may cause hyponatremia.
- *Liver:* carbamazepine causes an increase in total serum cholesterol, high-density, and low-density lipoproteins, which can induce an elevation of hepatic enzymes. However, routine monitoring does not appear indicated because the appearance of hepatitis is extremely rare.
- *Neurological:* carbamazepine, like many anticonvulsant drugs, may cause dizziness, ataxia, or diplopia.
- *Weight:* long-term, high dosage treatments with carbamazepine are associated with small degrees of weight gain.

Carbamazepine should be avoided during pregnancy because of the risk of neuronal cord malformations such as spina bifida. Moreover, the drug is transferred to breast milk in a concentration that is approximately 50% of that present in maternal plasma.

Carbamazepine overdose

Symptoms of carbamazepine overdose include drowsiness, stupor, coma, sinus tachycardia, atrioventricular conduction blocks, hypotension or hypertension, seizures, nystagmus, hyporeflexia or hyperreflexia, hypothermia, oral dyskinesias, and respiratory depression. Supportive interventions for overdose, include gastric lavage and instillation of activated charcoal until the patient is symptom-free.

Drug interactions

Carbamazepine is a potent inductor of the cytochrome P450 (mainly CYP3A4) and increases the rate of metabolism of a great variety of drugs (warfarin, lamotrigine, phenytoin, theophylline, valproic acid), decreasing their serum concentration and often reducing their therapeutic effects. Carbamazepine also increases the metabolism of oral contraceptives often reducing their effectiveness. Through autoinduction, after 2 to 3 weeks, carbamazepine increases the rate of its own metabolism. Conversely, many common drugs can increase the blood concentration of carbamazepine: erythromycin verapamil, diltiazem, isoniazid, and fluoxetine.

LAMOTRIGINE

Lamotrigine was developed as an antiepileptic drug, and it later showed to be useful in the treatment of a variety of neurological and psychiatric conditions. In particular, it has been found effective as maintenance therapy for Bipolar Disorder; it may also be somehow helpful in acute bipolar depression, whereas it is not effective in acute mania.

Pharmacokinetics

Lamotrigine is completely absorbed when administered orally. It has a 28-hour half-life, and it has a hepatic metabolism. Other anticonvulsants may strongly affect the pharmacokinetic properties of lamotrigine. In particular, valproate can inhibit its hepatic metabolism, whereas carbamazepine can induce it. The half-life of lamotrigine can thus vary from 14 to 56 hours when taken in combination therapies. It's important to consider co-treatments to choose a proper administration schedule for each patient (table XX)

Pharmacodynamics

It is not yet completely clear how exactly lamotrigine exerts its pharmacological action. It blocks voltage-sensitive sodium channels, affecting the realization of neurotransmitters glutamate and aspartate. It has also a mild effect on serotonin, dopamine, and norepinephrine reuptake in some animal models.

Therapeutic indications and clinical use

Lamotrigine is FDA approved for the treatment of epilepsy and as maintenance treatment of Bipolar Disorder. Its stabilizing effect seems to be stronger at delaying depressive episodes than manic ones. Moreover, it is mildly effective for the treatment of acute bipolar depression, while it does not have any clinically significant effects in the treatment of acute mania.

The table below shows the standard dosage of lamotrigine and as maintenance treatment of Bipolar Disorder. The dose should be adjusted considering co-therapies, and it can be further corrected by measuring the blood levels of the drug.

Table 9. Dosage of lamotrigine as a maintenance treatment in Bipolar Disorder

Dosage of lamotrigine as a maintenance treatment in Bipolar Disorder				
	Week 1 and 2	Week 3 and 4	Week 5	Target dosage
Monotherapy	25 mg/day	50 mg/day	100mg/day	200mg/day
With valproate	12.5 mg/day	25mg/day	50mg/day	100mg/day

With carbamazepine	50mg/day	100mg/day*	200mg/day*	400mg/day*

*divided doses

Side effects

The main concern about the treatment with lamotrigine is the risk of serious rashes, including Steven-Johnson's syndrome. Some risk factors may be age (pediatric patients show a higher risk) and overdose, that might be caused by an excessive intake or by some interaction with other drugs.

Minor skin rashes are observed in up to 10% of patients taking lamotrigine. The risk of a serious event should lead to the discontinuation of the drug whenever a rash appears. That is why the therapy has to be started at a low dosage, and for the first month any new drug, food or cosmetics should be avoided.

Generally, lamotrigine is very well tolerated. The most common adverse effects in patient affected by Bipolar Disorder and taking lamotrigine are insomnia, daily sleepiness, nausea, fatigue and back pain.

Due to the risk of seizures after discontinuation of the drug, lamotrigine should be tapered slowly when therapy needs to be stopped.

Lamotrigine is not indicated during pregnancy because of its *in vitro* effects on folate metabolism.

Drug interactions

Because of interference with lamotrigine hepatic metabolism, blood levels of the drug are decreased by the co-administration of agents such as carbamazepine and estrogens and increased by agents such as valproate and sertraline. That is why the administration schedule must be tailored for each patient (see Table 9).

11.4. ANTIPSYCHOTICS

Introduction

Until the 1950s, the management of chronic psychotic disorders was based primarily on assistance and support through institutionalization, with therapeutical attempts mainly related to the supposed effects of 'shock'-related therapies based on the use of cool water, agents producing elevate fever,

hypoglycemic states/‘insulinic coma’, and electroconvulsive therapy, with limited and not persistent results (ECT is still a valid option for resistant depression, but indication in chronic psychosis are very limited). The concept of "antipsychotic activity" arose accidentally from the observation of sedative effects after administration of chlorpromazine, originally prescribed as an adjunct to surgical anesthetics because of its body temperature lowering effect. Subsequently, chlorpromazine was successfully administrated to treat agitation in a manic patient with psychotic symptoms, surprisingly allowing the subject to resume normal life after 20 days of treatment.

This serendipitous finding represents the cornerstone of the game changing development of a pharmacotherapy for schizophrenia and led to the discovery and development of the so-called typical antipsychotics or first-generation antipsychotics (FGAs), which include phenothiazines, thioxanthenes, butyrophenones (haloperidol), and substituted benzamides. Originally, FGAs were defined as *neuroleptics* (according to the original presentation of chlorpromazine by Deniker in 1955 the term came from the Greek ‘which takes the nerve’) because their administration at high doses was associated with *neurolepsis*, charachterized by behavioral indifference and psychomotor slowing.

The development and introduction of clozapine in the 1970s represented the following milestone in the pharmacotherapy of schizophrenia, being the first atypical or second-generation antipsychotic (SGA). Although clozapine was initially temporarily withdrawn from the market due to tolerability issues (agranulocytosis, see below), during the following years the development and use of SGAs spread worldwide. Indeed, compared to FGAs, SGAs were found to be characterized by similar antipsychotic efficacy but better tolerability, and nowadays prescription of atypical antipsychotics is consistently higher in clinical practice.

The discovery and introduction of antipsychotics represented a radical turning point in both the history of mental illness and society. The introduction of FGAs into clinical practice led to a sharp decline in hospital occupancy, to progressive closure of mental asylums, and to the development of social policies concerned with mental health. Antipsychotics enabled patients affected by severe mental disorders to participate again in social life, greatly reducing the pressure on the health system and the impact of mental illness on society. Moreover the study of antipsychotic action shed new light not only on the neurobiological correlates of psychosis, but also on the neural basis of physiological brain functioning.

First generation (FGA)/Typical antipsychotics

Pharmacodynamics

FGA RECEPTOR ANTAGONSIM:

- D2
- Alpha-1
- M1
- H1

Antipsychotic efficacy of FGAs derives from blockage of dopaminergic D2 receptors (D2r), particularly in the mesolimbic dopamine pathway, which is primarily involved in the pathogenesis of positive symptoms. However, given the variable receptor distribution within the brain, in other cerebral areas (i.e. mesocortical and nigrostriatal pathways) D2r antagonism can determine significant side effects. The occurrence of these adverse effects is highly correlated with pharmacological load, and therefore the target dosage should always be the lowest effective.

Conventional antipsychotics possess affinities for muscarinic M1, histaminergic H1, and alfa-1 norepinephrine receptors, which can result in partially distinctive and overlapping side-effect profiles.

Efficacy

Large multicenter trials adopting evidence-based approaches failed to demonstrate significant differences in antipsychotic efficacy between the different FGAs. Nonetheless, antipsychotic response is characterized by high interindividual variability, and some patients might respond better to one conventional antipsychotic agent than another. This great heterogeneity depends on individual genetic and metabolic features that to date are only partially defined, and that can also influence duration of treatment, dosages, and associations with additional medications such as mood stabilizers, benzodiazepines, or antidepressant drugs.

Antipsychotic monotherapy at the lowest possible effective dose is recommended by international guidelines, especially at disease onset, since the administration of high dosages and/or of antipsychotic polytherapy is not supported by scientific evidence: exceeding the dopaminergic receptor saturation threshold (in general, at the net consideration of interindividual variability, a dose of about 5 mgs /day of haloperidol equivalent is already able to occupy D2 receptors to a degree related to clinical response in non-resistant patients) does not lead to further clinical benefits, but only increases the rates of side effects, especially extrapyramidal symptoms.

Haloperidol

Haloperidol is the progenitor of butyrophenone compounds. It was introduced in the 1970s but it is still one of the most prescribed conventional antipsychotic drugs because of its high antipsychotic potency and its relatively safe tolerability profile at low doses, which makes the drug easy to use. Indeed, haloperidol shows high affinity with D2r selectively but differs from other FGAs as it shows

low anticholinergic and antihistaminic activity. The therapeutic range is between 2 and 6 mg, greater doses are used in the acute psychotic phase to enhance sedative properties, mostly to manage behavioural abnormalities. Rarely doses over 6 mg show higher antipsychotic effect due to D2r saturation threshold. Haloperidol is characterized by a high lipophilia thus peak plasma concentrations occur after 1.7 to 6 hours after oral intake (bioavailability: 60-70%) and plasma protein binding is relatively high, settling around 90%. Metabolized in the liver by CYP3A4 and CYP2D6, excretion of metabolites occur preferentially through urine.

Concerning clinical indications, haloperidol is licensed for the treatment of acute and chronic schizophrenia and other psychotic disorders, delirium, psychomotor agitation within psychotic disorders or mania, mania, aggressiveness in Alzheimer o vascular dementia, Tourette syndrome or tic syndromes and Huntington disease when other treatments fail. It is widely used currently.

Chlorpromazine

Chlorpromazine, mentioned before as the first antipsychotic discovered, is a phenothiazine compound classified as a low-potency typical antipsychotic. Compared to haloperidol, it shows lower D2r affinity but higher antihistaminic and anticholinergic activity, respectively associated with sedation and muscarinic side effects. To date, chlorpromazine is rarely prescribed as antipsychotic monotherapy and mainly used in clinical practice for its sedative properties, or as an adjunctive treatment as antipsychotic enhancer drug.

The antipsychotic effect is reached with dosages over 200-250 mg, typically not more than 600 mg (maximum licensed dose 1000 mg), lower ones (25-75 mg) are used in clinical practice to induce sedation.

Concerning pharmacokinetic properties, the absorption is rapid after oral administration and the bioavailability of the drug is around 30-50% with high plasma protein binding. It is metabolized by CYP2D6 in the liver and it is excreted in the urine and bile. The half-life is highly variable ranging between 6 to 30 hours.

Clinical indications of the molecule are schizophrenia, paranoid delusional syndromes and substance-induced psychoses, delirium and mania. Other non-psychiatric indications are vomiting, incoercible hiccups and treatment of intense pain, generally in combination with other analgesics. It is also approved for pre-anaesthesia.

Zuclopenthixol

Zuclopenthixol belongs to the subgroup of thioxantens and like other FGA it presents good D2r affinity and, compared to haloperidol, also higher D1r affinity, thus showing a mixed D1/D2

antagonism. Indicated for schizophrenia treatment, it is largely used in intramuscular formulation, both long-acting (zuclopenthixol decanoate) and fast-acting vials (zuclopenthixol acetate) for the management of agitated behaviors by reason of its anticholinergic and sedative properties. In the clinical practice daily dosages range from 10 to 75 mg, associated with a strong antipsychotic activity and representing a valuable alternative to haloperidol. Concerning pharmacokinetics, like other antipsychotics, zuclopenthixol is characterized by rapid absorption after oral administration with a time to peak concentration of 4 hours, high serum proteins binding percentage and half-life is approximately 20 hours. Zuclopenthixol is approved for the treatment of acute and chronic schizophrenia and other psychotic syndromes and clinical conditions characterized by agitation or psychomotor excitement, hostility and aggressiveness. Moreover, it is also approved for the management of mania and organic mental syndromes accompanied by delirium and psychomotor agitation. It is still used currently in both pharmaceutical formulations.

Other typical antipsychotics:

Pimozide

Pimozide is a high potency FGA of the diphenylbutylpiperidine class, showing D2r blocking activity even greater than haloperidol, and is also antagonist at 5HT2r. Due to its low sedative properties at low doses, pimozide was the first antipsychotic considered as 'atypical', paving the way to study and development of antipsychotic effective on both negative and positive symptoms (see atypical antipsychotics section). Rarely prescribed for treating schizophrenia because of its tolerability issues concerning QT prolongation and extrapyramidal symptoms, this typical antipsychotic drug is mainly used for motor neurological diseases such as Tourette syndrome and resistant tics.

Perphenazine

Perphenazine is a piperazinyl phenothiazine showing a medium-potency antidopaminergic (D2r) activity, approximately ten times higher than chlorpromazine. Indicated for the treatment of schizophrenia, other psychotic disorders, and manic phases of bipolar disorder. Currently it is used infrequently, also in formulations with associate low doses of the drug with low doses of amytriptiline.

Thioridazine

Thioridazine is a FGA belonging to the phenothiazine drug group. Originally indicated and widely prescribed for schizophrenia treatment, and was effective in a wide range of psychotic conditions,

with a better EPS profile than haloperidol at low doses, but in the last yeardsin several countries the compound is no more available in most countries because of its high propensity to prolong the QT interval in a dose-dependent manner, thus inducing severe cardiac arrhythmias and in particular 'torsades de pointes'. Thioridazine shows high affinity for cholinergic receptors, thus producing significantly less extrapyramidal side effects than most FGAs.

Promazine

Promazine is a phenothiazine compound with very low antidopaminergic potency: despite it was originally included among antipsychotics at the beginning of the neuroleptic era, basically it is never used as antipsychotic, being instead widely used in the management of psychomotor agitation.

Second generation antipsychotics (SGA)/Atypical antipsychotics

Pharmacodynamics

As mentioned above, the distinguishing feature of SGAs is the serotonin antagonism elicited through 5HT2Ar blocking activity, which, in addition to anti-D2r properties, gives a peculiar "atypical profile" to these pharmacological compounds.

Given that serotonin physiologically inhibits dopamine release, the blockade of 5HT2Ar is associated with higher dopaminergic activity in the brain. However, 5-HT2A and D2 receptors show differential distribution according to the different brain areas, and the effects of the double dopaminergic/serotoninergic antagonism are variable throughout the brain, depending on receptorial density and SGA's receptorial binding profile. By blocking 5HT2Ar activity, atypical antipsychotics increase dopaminergic activity in nigrostriatal, mesocortical, and tuberoinfundibular pathways, but fail to reverse antipsychotic D2 antagonism in the mesolimbic system. Therefore, compared to FGAs, use of SGA should be associated with better neurological tolerability, lower rate of hyperprolactinemia, lower drug-induced negative/cognitive symptoms, and similar efficacy on positive symptoms.

However, although 5HT2Ar/D2r antagonism activity explains a large part of the atypical profile, it is not sufficient to understand all the pharmacological properties of SGAs. As an example, risperidone partially loses its atypical properties at higher dosages and induces hyperprolactinemia, and amisulpride is considered atypical, although lacking 5HT2A affinity and inducing hypeprolactinemia. Generally speaking, a drug is clinically considered as an 'atypical second generation' antipsychotic when showing a high antipsychotic efficacy (particularly on positive symptoms) and a low risk to

induce extrapyramidal side effects and hyperprolactinemia, but this association has a wide variety of manifestation depending on peculiar profiles on doses. Every antipsychotic displays a unique receptor binding profile that also includes affinities for other serotoninergic and dopaminergic receptors (i.e. 5HT2C, D1, D3, and D4), as well as for other neurotransmitter pathways such as noradrenergic, cholinergic, and histaminergic systems. Taken together, all the single receptor affinities determine the overall mechanism of action of every SGAs.

Efficacy

The introduction of SGAs was seen as a revolution in the treatment of schizophrenia. The innovation of SGAs was a serotoninergic/dopaminergic antagonist activity, associated with better extrapyramidal tolerability and that was also thought to be effective in ameliorating positive symptoms resistant to conventional antipsychotics. Moreover, initially major claims were also made concerning a possible better efficacy of atypical antipsychotics on negative and cognitive symptomatology, which could have revolutionized the treatment of schizophrenia.

Nowadays, with the sole exception of clozapine in resistant schizophrenia, large-scale studies and meta-analytic evidence now indicate no superior efficacy of SGAs over FGAs in treating positive, negative, and cognitive symptoms. Nonetheless, the introduction of SGAs undoubtedly represented a step forward in psychiatric clinical practice, leading to lower rates of iatrogenic EPS, and also reducing the impact of other significant side effects such as sedation and/or hyperprolactinemia. However, SGAs introduced the new issue of metabolic tolerability, as they are more frequently associated with metabolic syndrome, obesity, type 2 diabetes, dyslipidemia and cardiovascular side effects.

High variability characterizes receptor binding profiles of SGAs, resulting in significant differences in drug-related side effects and antipsychotic efficacy. The tolerability profile of each drug, along with specific and individual features, should be taken into consideration before choosing a certain antipsychotic for administration.

SGAs are usually preferred and recommended in the early stages of treatment (i.e., First Episode Psychosis), although they have similar antipsychotic efficacy to FGAs. Indeed, at the onset of the disease, young patients are more likely to experience acute neurological side effects, which should be avoided to favor pharmacological compliance and long-term clinical stabilization.

Risperidone and paliperidone

Risperidone is one of the most prescribed SGAs in clinical practice. It shows a high affinity for D2r and, at higher dosages, results similar to FGAs, potentially causing EPS and hyperprolactinemia. That

means that is should be used at low doses to obtain the highest potential benefit. Risperidone shows a high efficacy on positive symptoms of schizophrenia, and it is also commonly used in the management of elderly patients with psychosis, agitation, and behavioral disturbances associated with dementia. The incidence rate of metabolic adverse effects is lower compared to clozapine, olanzapine, and quetiapine.

Risperidone is extensively metabolized in the liver by cytochrome CYP 2D6 to 9-OH-risperidone also named paliperidone, its active metabolite. Over the last decade, paliperidone has been separately produced and marketed in oral and intramuscular long-acting formulations. Compared to risperidone, paliperidone shows similar efficacy but no hepatic metabolism and longer half-life, which makes it more suitable for patients with hepatic dysfunction.

Olanzapine

This SGA shows binding properties for several receptor classes and relatively lower affinity for D2r. It is thus associated with a lower rate of EPS and hyperprolactinemia, but its antihistaminic and serotonin 2C antagonist properties frequently determine metabolic side effects, being the SGAs most frequently associated with Metabolic Syndrome (together with clozapine).

Oral dose is rapidly absorbed and a relatively high percentage undergoes to a predominant CYP1A2 metabolism, but also CYP2D6 is involved to a lesser extent in the metabolism of the drug. Approximately, time to peak concentration is reached within 6 hours with 93% of serum proteins binding potential.

Olanzapine is indicated for the treatment of acute phases and maintenance of schizophrenia, moderate to severe manic episode and prophylaxis of manic or depressive episodes in bipolar disorder.

Quetiapine

Quetiapine shows a very atypical binding profile, virtually causing no EPS and prolactin elevations, and it is thus frequently used among patients with Parkinson's disease and L-Dopa-induced psychosis. Compared to risperidone and olanzapine is less effective in reducing positive symptoms, although there are psychotic patients that show a satisfactory antipsychotic response to this atypical compound. It is also prescribed for the treatment of bipolar disorder and in behavioural psychopathological symptoms in dementia. Quetiapine is associated with weight gain, as it strongly blocks histamine H1 receptors. Due to its anti-histaminergic properties, quetiapine is also used as a second-line treatment for insomnia. Depending on dosages prescribed quetiapine shows different effects ranging from anxiolytic and hypno-inducing properties (25-100 mg), in particular in organic and psychogeriatric conditions, to antipsychotic ones which are reached in a range from 400 to 800 mg.

Concerning pharmacokinetics, quetiapine is well absorbed after oral administration with a time to peak concentration of 1 hour and a half-life approximately of 6 hours.

Aripiprazole

Aripiprazole has a peculiar pharmacodynamics profile, acting as a partial agonist at the dopamine D2r and the serotonin 5-HT1Ar, and as an antagonist at the serotonin 5-HT2Ar. Differently from other antipsychotics, aripiprazole does not reduce dopaminergic activity by blocking D2r but modulates its activity according to pathway-related dopaminergic activity. Indeed, aripiprazole reduces D2r activity if dopamine transmission is overly active, whereas it increases neurotransmission in case of dopaminergic hypofunction. Aripiprazole has the propensity to induce akathisia but is much less frequently associated with other D2r related side effects such as EPS and hyperprolactinemia. Differently from other SGAs, aripiprazole is rarely associated with metabolic side effects. As quetiapine and olanzapine, beside schizophrenia it is also indicated in case of bipolar disorder, both as treatment maintenance and in the management of manic episodes. The common dosages used by clinicians range from 2,5-5 mg to 30 mg, which is the maximum dose approved. Aripiprazole is well absorbed after oral intake reaching maximum plasma concentrations in nearly 3 to 5 hours with a high percentage of molecules bound to plasma proteins (99%). Hepatic metabolism is mediated by CYP3A4 and CYP2D6.

Other atypical antipsychotics:

Brexpiprazole

Brexpiprazole is a new SGA recently approved for the treatment of schizophrenia and as adjunctive therapy for major depressive disorder. Similarly to aripiprazole, it is a partial serotoninergic and dopaminergic agonist. Brexpiprazole shows a higher affinity on 5HT1A/2A receptors, that explains its indication also for mood disorders. Its tolerability profile is similar to aripiprazole, characterized by a low risk for EPS, hyperprolactinemia, and metabolic alterations.

Cariprazine

Cariprazine is a recent antipsychotic indicated for the treatment of schizophrenia and bipolar disorder, which shows serotoninergic and dopaminergic partial agonism resembling the pharmacodynamics of aripiprazole and brexpiprazole. Studies suggest higher efficacy of cariprazine as monotherapy for schizophrenia with prevalent negative symptoms.

Amisulpride

Amisulpride shows peculiar pharmacological properties. Despite being considered a SGA, it belongs to substituted benzamides, characterized by a nearly absent serotoninergic antagonism and high specificity for D2 and D3 receptors. Low dosages of amisulpride selectively block presynaptic receptors resulting in a higher release of dopamine, thus leading to an antidepressant effect. At high doses, amisulpride block D2r activity and determine an antipsychotic effect. Amisulpride induces significant QT prolongation (careful ECG management is required) as well as hyperprolactinemia, but lower EPS than FGAs.

Ziprasidone

Ziprasidone was the fifth atypical antipsychotic marketed. It shares the anti-5HT2Ar and anti-D2r profile of other available atypical antipsychotics. Moreover, it shows 5HT1Ar agonistic activity and weak inhibiting properties of serotonin/norepinephrine reuptake. Metabolized in the liver by CYP3A4 and CYP1A2, its half-life is approximately 6-7 hours with an extensive serum proteins binding of 99%. Clinical indications are represented by schizophrenia and mania and therapeutic dosages range between 40 and 80 mg, with a maximum licensed dose of 160 mg.

Ziprasidone shows an optimal metabolic tolerability profile, as well as lower rates of hyperprolactinemia. However, ziprasidone has a significant impact on QTc, with an average prolongation of approximately 20 msec. Nowadays, it is infrequently prescribed.

Lurasidone

Lurasidone is approved for the treatment of patients with schizophrenia or bipolar depression; it is a potent antagonist of dopamine D2, serotonin 5-HT2A, and 5-HT7 receptors, and a partial agonist of 5-HT1A receptors. Lurasidone does not show any significant antihistaminic or anticholinergic activities and, thus, is not associated with metabolic alterations, sedation, or constipation, and some effects on cognition have been reported in literature. Its high affinity for D2r provides, on one side, good efficacy in treating positive symptoms, but, on the other, also a dose-related risk for akathisia, EPS, and hyperprolactinemia.

Pharmacokinetics of FGA and SGA

Antipsychotics are highly lipophilic, thus show high plasma protein binding. Peak plasma concentration generally is reached within 2-4 hours except for haloperidol which is more lipophilic. Typically, half-life ranges between 10 and 40 hours.

Concerning metabolism, antipsychotics are manly oxidized (CYP 450) or conjugated with glucuronic acid in the liver with the aim to increase hydrophilic properties for renal excretion.

Table 10. Pharmacokinetic of main antipsychotics

Antipsychotic	Tmax	Half-life	Time to steady state	Plasma Protein Binding (%)
Chlorpromazine	1–4	23-37 h	7 days	90%
Haloperidol	1.7-6.1 h	14.5-36.7 h	5 days	90%
Zuclopentixol	4 h	20 h	7 days	98%
Amisulpride	1–4 h	12 h	6-10 days	17%
Aripiprazole	3–5 h	75 h	14 days	99%
Clozapine	1.1-3.6 h	9.1-17.4 h	7–10 days	95%
Lurasidone	1.5–3 h	28.8-37.4 h	7 days	99%
Olanzapine	6 h	33 h	7 days	93%
Paliperidone	24 h	22 h	5 days	77%
Quetiapine	1–1.5 h	6–7 h	3 days	83%
Risperidone	1.6 h	3 - 22 h	5 days	89%

Therapeutic indications and clinical use of FGA and SGA

Nowadays, antipsychotics are commonly used in clinical practice for several conditions:

- Schizophrenia spectrum disorders;
- Mood disorders (acute mania, augmentation strategies in unipolar or bipolar depression, bipolar disorder maintenance treatment, adjunctive treatment of major depressive disorder with psychotic symptoms);
- Delirium;
- Severe behavioral problems (also in childhood and autism spectrum disorders) or aggression;
- Gilles de la Tourette syndrome.
- Augmentation strategies in obsessive-compulsive disorder (OCD).

Table 11. Daily dosage of main antipsychotics

Antipsychotic	**Starting (mg)**	**Maintenance (mg)**	**High Dosage (mg)**
Chlorpromazine	25	300-400	600-1000

Haloperidol	1	3–6	8-10
Zuclopenthixol	10	20-40	75-100
Amisulpride	25	400-800	1200
Aripiprazole	5	15-20	30
Clozapine	25	400*	800*
Lurasidone	37	74	148
Olanzapine	5	10–15	20
Paliperidone	3	6–9	12
Quetiapine	50	400-600	800
Risperidone	0.5	3–5	6-8

*mean dose, prescription should be based on clozapine's plasmatic levels (range: 350-600 ng/mL)

Side effects of FGA and SGA

Extrapyramidal symptoms (EPS) and pseudo-Parkinsonism

Antagonism of dopaminergic neurotransimission in the nigrostriatal pathway can lead to neurological motor side effects named extrapyramidal symptoms (EPS).

EPS are:

- Dose-related.
- Most likely with high doses of FGA.
- Less common with SGA, particularly clozapine and quetiapine.

These symptoms, resembling those observed in Parkinson's disease (and therefore defined as "iatrogenic parkinsonism"), include akinesia, bradykinesia, tremors, rigidity, and acute dystonia. Long-term antipsychotic treatment, particularly with FGAs, can also induce the development of tardive dyskinesia, which is one of the most insidious side effects of antipsychotics, highly interfering with daily functioning and quality of life and often irreversible.

The time of presentation of acute EPS is usually days to weeks after antipsychotic drugs are started or the dose is increased, whereas the onset of tardive dyskinesia may occur even after years of treatment.

Treatment: reduction of the antipsychotic dose, switch to an antipsychotic with lower propensity to induce EPS (lower D2r affinity) or prescription of an anticholinergic medication are therapeutic options that need to be considered. When none of these options result effective, antipsychotic switch to clozapine, whose other indication is schizophrenia intolerant to treatment, beside resistance, is often resolutive.

ANTICHOLINERGIC AGENTS

In the nigrostriatal pathway a reciprocal interconnection exists between dopamine and acetylcholine.
Dopamine resizes acetylcholine activity: if dopamine receptors are blocked, acetylcholine becomes overly active contributing to EPS.
Anticholinergic drugs reduce EPS decreasing acetylcholine activity.

Table 12. Extrapyramidal symptoms

EPS	Symptoms	Onset	Mechanism	Prevalence
Acute dystonia	Acute EPS: Muscular spasm, typically of tongue, eyes, face, neck	Hours/days	Unknown	2,5-5%
Akathisia	Subacute EPS: Inner tension and restlessness; inability to sit still or remain motionless	Days 1-60	Unknown	25%
Parkinsonism	Subacute EPS: Tremor, hypokinesia, muscular rigidity rigidity, postural instability, amimia	Days 5-30	DA antagonism in basal ganglia	20-40%
Tardive dyskinesia	Involuntary and spontaneous muscular movements.	Years	DAr supersensitivity	20-30% Annual incidence: 4-5%

Acute dystonia

Uncontrolled muscular spasms can occur within hours to days after antipsychotic treatment is started, more frequently using FGAs. Intramuscular or intravenous administration can induce dystonic contractions within minutes. Common manifestations are oculogyric crisis, spasmodic torticollis, mandibular or buccal dystonia, blepharospasm, limbs, and back pain. The two most concerning presentations are laryngospasm, rare but life-threatening, and oculogyric crisis, a highly distressing tonic and recurring deviation of the eyes.

Treatment: depending on the severity of symptoms, anticholinergic drugs can be administered intramuscularly or (with extreme caution and in the most severe cases, due to cardiological risk of injecting an anticholinergic) intravenously, as well as intravenous benzodiazepines. Subsequent

switching to an antipsychotic with a low propensity to induce EPS is recommended as patients who experienced acute dystonia are more vulnerable.

Akathisia

Most antipsychotics (both FGA and SGA) can induce a subjective sense of mental unease, a inner feeling of tension, and observable motor restlessness. Typically, it is observed an inability to remain still and to maintain postions, 'on-site' march, and sometimes also psychiatric symptoms such as anxiety, dysphoria, and self-aggressiveness. Akathisia is a relatively common adverse effect experienced hours to weeks after antipsychotic treatment is started.

Treatment: besides common techniques adopted to avoid EPS (antipsychotic switch or dose reduction), an effective strategy is to use benzodiazepines such as clonazepam or add propranolol. Notably, anticholinergic medications are generally unhelpful unless akathisia is associated with a iatrogenic parkinsonian syndrome.

Tardive dyskinesia

A chronic blockade of D2 receptors in the nigrostriatal dopaminergic pathway secondary to long-term antipsychotic administration can induce a hyperkinetic movement disorder known as tardive dyskinesia (TD), a late-onset extrapyramidal syndrome. Typically, TD affects facial muscles (small muscles), causing grimacing, buccal, and tongue movements such as tongue protrusion or constant munching. Limb movements, particularly evident in distal areas, are less common. Severe orofacial dyskinesia is highly disfiguring and may greatly interfere with speech, eating, swallowing, or breathing, while truncal dystonia can be extremely distressing and interfere with gait and mobility. Respiratory dyskinesia may produce tachypnea, irregular breathing rhythms, and grunting noises that are commonly misinterpreted as primary respiratory problems.

Etiopathogenesis of TD has not been fully understood yet, however most consistent evidence suggest that chronic antipsychotic treatment lead to a dopamine receptor supersensitivity, and to an imbalance between dopamine type 1 (D1) and type 2 (D2) receptors related activities in the basal ganglia.

The incidence of TD is about 5% for every year of conventional antipsychotics treatment maintenance, whereas SGAs are associated with a lower incidence of TD than FGAs, with an annual incidence rate approximately 25% lower and is absent or questionable with clozapine.

TD is sometimes reversible, indeed early identification and suspension of antipsychotic, lead to symptom remission in 50 to 90% of patients, especially among young subjects. However, it is to note that several months are usually needed for TD remission, sometimes up to three years after antipsychotic discontinuation.

Treatment: switch to another antipsychotic with low D2r affinity: clozapine is the first choice drug, being associated with higher rates of symptomatic resolution (the effects seems to be active due to the balance of D1 and D2 receptor blockade of this drugs, beside the low d2 activity in general). Interestingly patients with tardive dyskinesias are frequently also resistant to typical antipsychotic and for this reason may have been exposed to higher cumulative doses, with is a risk factor itself: when prescribed clozapine improves usually both resistant symptoms and tardive dyskinesia). Clozapine is also effective in treating a great number of tardive dystonias, the most resistant manifestation of long-term motor side effect of antipsychotics.

When contraindicated, quetiapine represents a possible antipsychotic alternative to clozapine. In tardive dystonia tetrabenazine, velbenazine, or deutetrabenazine may represent valid add-on treatments.

Hyperprolactinemia

Anti-dopaminergic properties of antipsychotics account for the disinhibition of prolactin release in the tuberoinfundibular pathway through the removal of the inhibition induced by dopamine. Increased plasma concentrations of prolactin identify a condition defined as hyperprolactinemia, which is a common side effect of antipsychotic treatments, although in clinical practice it is frequently underdiagnosed and treated only when symptomatic. Symptoms vary according to patient's sex. Typical females' symptoms are galactorrhea (breast secretions), oligomenorrhea and amenorrhea, vaginal dryness, dyspareunia, and decreased libido as well. Similarly, males can show gynecomastia (rarely galactorrhea), impotence, and decreased libido too. Hyperprolactinemia may also interfere with fertility, particularly in women.

The relationship between prolactin concentrations and occurrence of clinical symptoms of its elevation is linear, although there is high clinical variability of symptoms prevalence and severity between subjects and different antipsychotics. It is important to check for prolactin levels and related symptoms related due to different reasons including compliance, as sexual side effects are strongly related to bad compliance in (particular in young males), and health in general, as higher levels are associated with weight gain and reduced bone density (particularly in women), whereas a link with breast cancer has not yet clearly demonstrated, although suggested in some studies.

Treatment: First-line treatment is switch to other antipsychotics with a low risk of inducing hyperprolactinemia (clozapine and aripiprazole in particular). Other strategies include additional treatment with low doses of aripiprazole (partial D2 receptors agonist), or with very low-dosage of cabergoline (dopamine agonist) given weekly or biweekly. This latter strategy may however lead to

a psychopathological worsening at higher doses or daily dosing and should be considered only if other approaches fail.

Neuroleptic malignant syndrome (NMS)

The neuroleptic malignant syndrome is a rare but potentially life-threatening acute disorder of thermoregulation and neuromotor control that can cause an emergency condition characterized by an extreme and generalized muscular rigidity associated with hyperpyrexia, dysautonomia, change in mental status/consciousness, renal failure and even death. Rhabdomyolysis, myoglobinuria, creatine kinase (CK) elevation and neutrophilia are usual laboratory findings.

Among patients taking antipsychotics incidence of NMS ranges from 0.02 to 3%. Again, D2 receptors antagonism is thought to be the leading pathogenetic mechanism, in particular the central dopamine receptor blockade in the hypothalamus that could lead to hyperthermia and other dysautonomic symptoms. Genetic predisposition (familiarity), high potency FGA, polypharmacy, dehydration, and male gender, are listed among the main risk factors. Although less frequently, atypical NMSs induced by low-potency anti-dopaminergic agents are also reported, characterized by a different clinical presentation with tachycardia, mental status changes, and diaphoresis, but not including rigidity. Early diagnosis and treatment significantly improve prognosis of NMS, that is characterized by and mortality rates ranging from 5 to 20%. Acute renal failure induced by rhabdomyolysis and myoglobinuria is considered the most serious independent predictor of mortality Therefore, severe manifestations require intensive care unit monitoring and treatment in order to avoid permanent morbid sequelae and death. When NMS is successfully treated, symptom remission usually occurs within 10 days, although sometimes residual catatonia and motor signs are reported up to 6 month after onset, especially among patients treated with LAIs.

Treatment: removal of the causative antipsychotic agent, rehydration (cold intravenous fluids), benzodiazepines and administration of bromocriptine and/or dantrolene.

Other side effects

Haloperidol has relatively low anticholinergic or antihistaminic binding properties

As previously discussed, D2 receptors antagonism is the main pharmacodynamic activity of antipsychotics, but both FGAs and SGAs shows several other receptor binding properties associated with both clinical effectiveness and drug tolerability. Every antipsychotic has a unique receptor binding profile, and therefore can lead to different possible side effects according to its pharmacodynamics properties.

Muscarinic cholinergic antagonism

The ability of antipsychotics to block muscarinic cholinergic receptors can lead to several adverse effects such as constipation, cognitive blunting, dry mouth, and blurred vision. The entity of cholinergic blockade may explain the lesser propensity of some antipsychotics to induce extrapyramidal symptoms, given the "brain balance" between dopamine and acetylcholine. Specifically, fewer EPS are correlated with stronger anticholinergic properties. On the other hand, a strong cholinergic blockade can worsen the cognitive impairment of schizophrenia or precipitate a delirium or a cognitive disorder.

Treatment: dosage reduction or switch to another antipsychotic with lower anticholinergic affinity.

Histaminic antagonism

Several FGAs and SGAs have an antihistamine activity leading to side effects such as weight gain and sedation. Sedative properties vary across antipsychotics representing both a side effect, if sedation is unwanted, and/or a therapeutic effect in case of aggressive behavior or insomnia.

Treatment: dosage reduction or switch to another antipsychotic with lower histaminic affinity.

Alpha-1-adrenergic antagonism

Alpha-1 adrenergic blocking activity can lead to cardiovascular side effects such as orthostatic hypotension, dizziness, tachycardia, and drowsiness.

Treatment: dosage modulation, or addition of alpha-1-agonists (midodrine) counteracting orthostatic hypotension through vasopressor and anti-hypotensive properties. To treat tachycardia beta-blockers are often prescribed.

ECG alteration: QT prolongation

Several antipsychotics, both FGAs and SGAs, are associated with prolongation of QT interval. Extreme QT prolongation is associated with increased risk for developing of polymorphic ventricular tachycardia, a peculiar life-threatening cardiac arrhythmia also defined as torsades de pointes. Pimozide, ziprasidone and amisulpride have the highest increasing effect on QT interval, while aripiprazole and lurasidone are considered the safest. Among the others, SGAs, haloperidol and chlorpromazine have a moderate propensity to induce QT prolongation, although there is great variability among atypical antipsychotics. Electrolyte disorders (sodium, potassium, magnesium) are associated with higher risk of cardiac arrhythmia, as well as use of concomitant drugs known to prolong the QT interval such as antiarrhythmics, macrolide and fluoroquinolone antibiotics, some antifungal and antiviral drugs, and TCAs. In this context, pharmacological associations require

particular attention, since concomitant treatment may also alter antipsychotic metabolism leading to higher plasmatic concentrations and thus further increasing risk of QTc prolongation.

QT interval changes according to the heart rate, shortening as heart rate increases. Therefore, proper evaluation of cardiac tolerability should include the examination of QT controlled for heart rate (QTc), in order to evaluate standardized values. Moreover, sex related differences must be take into account as well, since women physiologically exhibit longer QTc intervals.

When a patient shows a basal QT prolongation, SGAs with a low propensity to interfere with cardiac conduction should be prescribed (e.g., olanzapine, aripiprazole, and lurasidone).

Metabolic side effects

Antipsychotics, especially SGAs, are burdened by metabolic side effects that negatively impact long-term prognosis and life expectancy. Weight gain is indeed frequently associated with atypical treatments, typically occurring from the early phases of the treatment: the most substantial weight gain is observed among antipsychotic naive patients after the first 6 weeks of treatment, usually reaching a plateau along the course of the illness. Unfortunately, weight gain is frequently hard to reverse, even after switching to more weight-neutral antipsychotics. The underlying mechanism is not fully understood, and the weight gain does not seem dose-dependent. Nevertheless, it is a matter of fact that clozapine and olanzapine show the greatest affinity for 5-HT2C and H1 receptors and have the greatest weight gain potential, making these receptors plausible mediators of the pathogenetic process. Altered glycemia, type II diabetes, or worsening of pre-existing diabetes are other metabolic adverse effects that can occur even regardless of weight gain. Moreover, alterations of lipid homeostasis are frequently reported during antipsychotic treatment, characterized by an increase in circulating levels of low-density lipoprotein (LDL) and triglycerides, and decreased levels of high-density lipoprotein (HDL) cholesterol.

The aforementioned metabolic alterations together contribute to the establishment of a condition defined as metabolic syndrome, associated with an increased risk for cardiovascular disease and type 2 diabetes mellitus. It is to note that schizophrenia is associated with metabolic and cardiovascular risk factors (sedentary lifestyle, poor quality food intake, high rates of smoking) regardless of antipsychotic medications.

Prevention and treatment of metabolic side effects and metabolic syndrome are based on aerobic exercise and diet. Moreover, dopamine partial agonists (i.e., aripiprazole), ziprasidone, and lurasidone have minimal adverse effects on metabolic parameters and may represent potential alternative treatments in case of severe metabolic alterations.

Table 13. Metabolic side effects of main atypical antipsychotics

Agent	Weight gain	Dyslipidemia	Diabetes
Amisulpride	+	-	+
Aripiprazole	+/-	-	-
Clozapine	+++	++	+++
Lurasidone	-	-	-
Olanzapine	+++	++	+++
Quetiapine	++	+	++
Paliperidone	++	+/-	++
Risperidone	++	+/-	++

Clozapine: the atypical SGA

Clozapine was the first licensed and marketed SGA in the 1970s and, to date, still represents the most effective and atypical SGA in resistant schizophrenia, although its precise mechanisms of action are not fully understood yet.

Clozapine is the only antipsychotic with a demonstrated efficacy in treatment-resistant schizophrenia (TRS).

TRS

Insufficient response to sequential treatment with at least 2 antipsychotics (FGA or SGA)

Clozapine has a unique receptorial binding profile, characterized by low D2r affinity relatively high affinity for D1 receptors and higher anti-serotoninergic properties, showing the highest 5HT2A/D2 ratio. Moreover, differently from other antipsychotics, clozapine is a glutamatergic agonist at NMDA receptors. This peculiar activity may underlie its superior efficacy in TRS.

Nevertheless, to date, clozapine is not yet considered a first-line treatment due to its peculiar tolerability profile. Indeed, besides dopaminergic, serotoninergic, and glutamatergic activity, clozapine also shows a high affinity for histaminic, cholinergic, and adrenergic receptors, leading to a wide range of side effects. Moreover, it is also associated with the risk of a rare but severe hematological complication called agranulocytosis, a severe form of granulocytopenia.

Low titration of clozapine is a good clinical practice to avoid several adverse effects

Still, due to its low propensity to induce EPS, clozapine has two additional indications. First, it represents the only indicated and effective treatment for patients with schizophrenia developing

severe neurological side effects such as tardive dyskinesia. Second, it is recommended for patients with comorbid psychotic disorders and Parkinson's disease.

Side effects of clozapine

Agranulocytosis/granulocytopenia

In 1975 Clozapine was withdrawn because of its association with agranulocytosis, a severe side effect that occurs in about 0,5-2% of patients, with up to 3% of patients that may develop neutropenia. In 1988, the publication of Kane and colleagues concerning the higher efficacy of clozapine among TRS patients paved the way to its reintroduction in clinical practice, although strictly monitored and limited to TRS. Since then, patients must have their blood count monitored weekly for the first 18 weeks of treatment (over 80% of cases occur within this period), then every month for as long as they are treated with clozapine, although worldwide there are variations among monitoring recommendations as well as granulocytes threshold for clozapine cessation. Almost 30 years after clozapine reintroduction, to date large scale studies indicate that the risk of hematological adverse effects decreases along with the duration of the treatment and with age, with 85-90% of cases occurring within 1 year after clozapine introduction. Consistently, it is esteemed that after one year of treatment the risk of agranulocytosis is comparable with that of other antipsychotics. Based on this evidence, different researches proposed a revision of clozapine-related surveillance protocols (not yet done), suggesting a less strict monitoring after 1 year of treatment.

Associations between clozapine and carbamazepine are to be avoided due to increased risk of agranulocytosis

Cardiac side effects

Tachycardia. It is a very common side effect, especially during the first four weeks of treatment. It is usually benign but sometimes may persist, requiring medication with beta-blockers.

QT prolongation. With respect to other FGAs and SGAs clozapine is relatively safe, however clozapine has been associated with possible dose-dependent QT interval prolongation.

Myocarditis. The most feared cardiovascular side effect is clozapine-induced myocarditis, a hypersensitivity response, eosinophil-mediated, hesitating in myocardial inflammation. Despite subclinical inflammation, identified by elevation of troponin, is a relatively frequent finding, particularly in the early phases of treatment, myocarditis is an emergency that requires immediate clozapine cessation. The incidence of myocarditis is debated, ranging from 1% to 3% of clozapine users. Myocarditis is most likely to occur within the first 6-8 weeks of treatment (80-90% of cases),

although cases during chronic treatment are also described. Rapid dose titration, older age, male sex, and concurrent medication with other compounds such as sodium valproate appear to be risk factors.

MYOCARDITIS AND CLOZAPINE

Clinical features
Symptoms: fever, hypotension, fatigue, tachycardia, dyspnea, and chest pain.
Laboratory findings: C - reactive protein (CRP) and troponin elevation and eosinophilia.
Diagnostic gold standard: echocardiography and cardiac magnetic resonance.

Monitoring
Daily: pulse, blood pressure, temperature, respiratory rate, subjective reports of symptoms.
Weekly: CRP, troponin, full blood count, ECG if possible.
Discontinuation of clozapine and investigation through echocardiography or MRI are recommended if either troponin exceeds twice the upper limit of normal or CRP is more than 100 mg/L.
If raised troponin or CRP not as above: maintenance of treatment and daily CRP and troponin monitoring.

Hypersalivation (Sialorrhea)

Like other antipsychotics, clozapine shows muscarinic antagonism on M1, M2, M3, and M5 receptors but it is also a full agonist on the M4 subset, highly expressed in salivary glands. Despite pharmacological bases remain unclear, the agonist activity on M4 receptors is thought to be the mechanism underlying hypersalivation. Other plausible explanations are adrenergic alpha-2 antagonism or inhibition of the swallowing reflex. Hypersalivation occurs in almost 30% of patients treated with clozapine and negatively impacts quality of life, sometimes leading to drug discontinuation.

Gastrointestinal hypomotility

An under-recognized and potentially life-threatening adverse effect of clozapine treatment is gastrointestinal hypomotility, which can hesitate in severe constipation, paralytic ileus, and obstruction. Older age, female sex, obesity, and high doses of clozapine are among the risk factors for gastrointestinal hypomotility.

Seizures

Clozapine lowers the seizure threshold in a dose-related manner, especially if rapid dose escalation occurs. For this reason, it is not recommended in patients suffering from epilepsy.

Antipsychotics: Pharmacological Interactions

Main drug interactions of antipsychotics are related to the cytochrome P450 (CYP) pathway. Concomitant administration of CYP inducers and inhibitors may lead to increases and decreases of antipsychotic plasma concentrations, thus altering drug clinical efficacy and tolerability. Among psychiatric drugs, SSRIs such as paroxetine and fluvoxamine strongly inhibit CYP, leading to higher antipsychotic plasma concentrations, whereas antiepileptic mood stabilizers, especially carbamazepine are known to induce CYP and to decrease FGA and SGA plasmatic levels. Smoking should be also be taken into account, as it can induce CYP dose-dependently.

Beside potential variations in plasmatic concentrations, when prescribing antipsychotics clinicians should be always aware of the individual tolerability profile of each FGA/SGA in order to avoid potential cumulative tolerability issues with other concomitant drugs (i.e. antiarrhythmics and QTc prolongation). In this view, administration of antipsychotics with sedative properties (i.e. clozapine, olanzapine, and chlorpromazine) should be carefully administered in combination with other CNS depressants.

BOX: SEDATION AND AGITATION

Different compounds have sedative properties, usually perceived as side effects (sedation) but useful in clinical practice to induce sleep or manage agitation. Antipsychotics' sedative properties are dose-dependent and proportional to H1r and 5HT2Ar antagonism.

Antipsychotics' propensity to induce sedation is:

- Very high for clozapine, chlorpromazine;
- High for quetiapine, olanzapine, asenapine;
- Moderate for haloperidol, risperidone, lurasidone, aripiprazole (high dose);
- Low for paliperidone;
- Very low/absent cariprazine, amisulpride.

In clinical practice, Promazine (FGA) is widely used for the management of aggressiveness or agitation.

Quetiapine, at very low doses, is an off-label option for the treatment of insomnia. Guidelines recommended quetiapine only in patients with specific comorbid psychiatric disorders when other strategies have failed.

Benzodiazepines (BDZ) have also a sedative effect depending on dose and way of administration. Intramuscular administration of BDZ is commonly used alone or in co-administration with antipsychotics in aggressive/agitated patients to induce sedation.

BDZ are efficacious for sleep disturbances in elderly people but increase the risk of cognitive impairment, ataxia, and motor disturbances.

Molecules with primary antihistaminic properties (hydroxyzine) are useful tools to induce sedation/drowsiness, thus overcoming insomnia. Intramuscular co-administration with antipsychotics is a common practice to obtain sedation (i.e. promethazine + haloperidol). Notably, antihistaminic compounds prolong QT interval similarly to antipsychotics.

According to guidelines, management of agitation depends on the related causes and features. If agitation is associated with delirium but not with substance withdrawal, BDZ should be avoided, preferring low dose antipsychotics (i.e. risperidone, haloperidol). In presence of substance withdrawal, oral and parenteral BDZ should be prescribed, possibly associated with antipsychotics as second line treatment. Agitation not associated with delirium but with psychosis should be treated using oral/intramuscular antipsychotics as first-line treatment, eventually associated with BDZ (oral or parenteral).

BOX: LONG-ACTING INJECTABLES (LAI) - DEPOT ANTIPSYCHOTICS

LAIs (depot antipsychotics) are frequently prescribed to improve adherence, especially in subjects with poor insight and pharmacological compliance, and are highly effective for maintenance treatment. There are no significant differences in efficacy between oral and depot formulations, neither in FGA nor SGA depots. Before starting treatment with LAI, when possible, the oral formulation should be administered for a brief period in order to evaluate antipsychotic response and tolerability. Haloperidol, risperidone, paliperidone, aripiprazole, and olanzapine are the LAIs most frequently used in clinical practice. Time administration interval for LAIs administration is usually 28 days, but can range from 15 days (risperidone) up to 3 months (paliperidone), according to the different antipsychotic.
Notably, there are two different long-acting formulas for paliperidone (28 days or 3 months)

Suggested Readings

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