

A Review on Management of Psychosis using Pharmacological Strategies

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Abstract

Psychosis are very common in medical problem about Forty percent of the people that, have anxiety or depression which are associated to physical illness. By which, psychiatric problem is an important part of medical attention and many people usually have psychiatric drugs associated to other treatments. In reality, research which is to be done in Nineteen Seventy-Four demonstrated that integrated therapy (i.e. combined use of medication and psychotherapy) is not harmful to the patient, but is actually useful. However, the conflict between pharmacotherapy and psychotherapy had already made a great disservice to patients, sometimes delaying the required drug treatment (e.g. the importance of duration of untreated psychosis for the prognosis of schizophrenia) or other avoiding effective psychological interventions that could lead to a better quality of life and reduce the risk of suicide. This may be the case when considering dialectical behaviour therapy or exposure and response prevention techniques in cognitive behavioural therapy for borderline personality disorder and obsessive compulsive disorder, respectively. Unfortunately, today, despite a much-vaunted integration of treatments, on the one hand we often deal with reductionist attitudes that judge psychotherapy as irrelevant and consider drug therapy alone sufficient for treatment.

Keywords: Borderline personality disorder, Cognitive behavioural therapy, Obsessive compulsive disorder, Dialectical behaviour therapy, Psychotherapy, Psychosis

Abbreviations: DBT: Dialectical Behavior Therapy; ERP: Exposure and Response Prevention; CBT: Cognitive Behavioral Therapy; BPD: Borderline Personality Disorder; OCD: Obsessive-Compulsive Disorder; SSRI: Serotonin Selective Reuptake Inhibitors; AP: Antipsychotics

Introduction

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

Antidepressants

These drugs act on depressive illness through the action on various neurotransmitter systems: serotonin, noradrenaline and

dopamine. The most used of these are SSRI (serotonin selective reuptake inhibitors), because of their efficacy and good profile of side effects.

Antipsychotics

They are used in the control of psychotic symptoms and as major tranquilizers. Antipsychotics are classified on first generation and second generation. The first of them act upon dopamine receptors and the second ones upon serotonin and dopamine receptors to have antipsychotic effects. These second-generation substances have less side effects and a different profile of action.

Anxiolytics

The most widely used are benzodiazepines, which act upon a specific GABA receptor. This family of drugs has a very quick effect, but they aren't recommended for a long time use because they can produce dependence and their effects are limited. They are also used like anticonvulsants.

Antiepileptics

This group of drugs is used in psychiatry for the maintenance and control of bipolar disorders, and they are useful too like anti aggressive drugs. The therapeutic drug monitoring is necessary when some of these substances are administrated because of their

potential toxicity and the pharmacological interactions with other treatments.

Lithium

It is a salt used for control of manic symptoms and maintenance of bipolar disorders. Its action mechanism is unknown, despite its usefulness and generalized utilization. It's necessary to control its plasmatic level into a tight range to avoid toxicity and to achieve its function.

Other drugs widely used in psychiatric disorders: methadone, anticholinesterases, stimulants, alcohol aversive are also important due to their side effects and their pharmacologic interactions [1].

Antidepressants

First antidepressant drugs were a casual finding and they affect to various neurotransmitters systems. Usually these old drugs produce many secondary effects. Afterwards, some hypotheses have emerged about the neurotransmission implicated in depression (monoamines: serotonin, noradrenalin and dopamine). Drug development progresses in parallel to this investigation so more selective drugs appeared as Selective Serotonin Reuptake Inhibitors, (from now on SSRIs), ameliorating secondary effects. Antidepressant classification depends on the assumption of their action mechanism. Following that schema, there are eight different pharmacological mechanisms at least. Most of the antidepressants block monoamine reuptake, but others block alpha-2 receptors or monoaminoxidase enzyme [2].

Monoamine reuptake inhibitors

Tricyclic and tetracyclic antidepressants (TCA)

The tricyclic and tetracyclic branch of antidepressants has a demonstrated and high efficacy, only limited by their sedative and anticholinergic effects. They act on a huge number of receptors, and

are cardiotoxic in case of overdoses, as anticholinergic toxicity and convulsions.

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

Main therapeutic indications

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

- i. Panic disorder.
- ii. Generalized anxiety disorder.
- iii. Obsessive-compulsive disorder: clomipramine especially. None of the others seems so effective.
- iv. Others: Alimentary conduct disorder and pain disorder.

Serotonin Selective Reuptake Inhibitors (SSRIS)

Serotonin is a neurotransmitter especially relevant in neurobiological basis in affective disorders, compulsive-obsessive disorder, and aggressive behavior. SSRIs block the serotonin reuptake bombs action, augmenting serotonin concentration in synapsis and post synapsis receptors' occupation. Though this effect appears early during treatment, clinical effects delay 3-6 weeks. They are metabolized at liver, present a low affinity except for serotonin receptors, are enough sure in overdoses, change sleep structure (reduce latency and total amount of REM sleep) and might be avoid used with MAOIs, due to the risk of serotonergic syndrome.

a) Therapeutic indications: Depression; Anxiety disorders, including Obsessive-Compulsive Disorder, Bulimia nervosa, Psychosomatic disorders [3].

Noradrenalin selective reuptake inhibitors

It selectively inhibits the reuptake of norepinephrine, but it has little effect on the reuptake of serotonin or dopamine. It is structurally related to fluoxetine. It has little affinity for muscarinic receptors or cholinergic and does not interact with the alfa1, alpha2, adrenergic beta, serotonergic, dopaminergic or histaminergic receptors. Therefore, SSRIs and reboxetine have

some complementarity effects and are used together in the clinic in some resistant depressions.

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

Inhibitors of the reuptake of serotonin and norepinephrine

Venlafaxine

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

Duloxetine

Like venlafaxine, it inhibits the reuptake of both serotonin and norepinephrine, Duloxetine has a minimal affinity for dopamine and histamine receptors. It has significant hepatic metabolism, with many metabolites. It's a moderate inhibitor of CYP 2D6. Its excretion is renal [4].

Inhibitors of the reuptake of norepinephrine and dopamine (bupropion)

It is usually more effective on symptoms of depression than anxiety and quite useful in combination with SSRIs. It has some dopaminergic effects and therefore can induce mild psychostimulant effects. The mechanism of action is not known with accuracy. It seems that weakly inhibits the reuptake of dopamine, raising levels of it in the nucleus accumbens. This increase in dopamine levels in the "area of reward" of the brain may be responsible for the use of bupropion in the cessation. Some data indicate that it exerts its antidepressant effects

increasing the functional efficiency of the noradrenergic systems. Apparently, it has no effect on the serotonin system, so it is not effective to block panic attacks.

Serotonergic modulators: Trazodone

Its mechanism of action is the modulation of serotonergic neurotransmission; it is a relatively specific inhibitor of the reuptake of serotonin. It does not cause any anticholinergic effects. It has Alfa1 adrenergic antagonism and antihistaminergic activity, so

has more sedative effects than other antidepressants. The sedative effects appear to one hour after administration and antidepressant effects at 2-4 weeks.

Monoamine Oxidase Inhibitors (MAOIs)

They inhibit the enzyme MAO, who is responsible for the oxidative deamination of neurotransmitters such as serotonin, norepinephrine, or dopamine. There are two ways for MAO enzyme: MAOa and MAOb. The MAOa metabolizes the monoaminergic neurotransmitters more closely associated with depression (norepinephrine and serotonin). The MAOb acts upon some aminergic substrates, called protoxins, toxins that can cause neural damage. Therefore, the inhibition of the MAOa is associated both hypertensive effects and therapeutic effects. Inhibition of the MAOb is associated with the prevention of neurodegenerative disorders, such as Parkinson's disease processes. The MAO is widely distributed in the body. The blockade of the MAOa in the gastrointestinal tract is responsible for the "cheese effect". It consists of a severe hypertensive crisis that occurs in patients who are taking MAOIs and ingest food containing tyramine. Tyramine is usually metabolized in the digestive tract but the blocking of the MAOa allowed their passage into general circulation. So, patients in treatment with IMAOs must follow a tyramine-restricted diet. They exert their effects primarily in the CNS. They act on the mood, decreased sleep and insomnia and daytime sleepiness. They are characterized by a significant reduction of REM sleep. The MAOIs are not considered antidepressants in frontline due to restrictions in the diet, its pharmacological interactions and its broad side effect profile.

Classic and second-generation antipsychotics

Classic antipsychotics

Among classic antipsychotics (AP) there is no one that has a clear superiority over the others, so choice must be made depending on previous response or side effects profile. The AP are well absorbed orally, although their bioavailability is altered with the intake of certain foods, coffee, calcium antacids and excessive consumption of nicotine, which can reduce the absorption from the intestinal tract. They have great solubility and easily cross the blood-brain barrier. Classic antipsychotics include: Clorpromazine, levomepromazine, flufenazine, perfenazine, trifluoperazine, haloperidol, zuclopentixol, molindone, and pimocide. The AP show a great affinity for plasma proteins (85-90%), which involves risk of toxicity when other drugs that also bind to proteins are running simultaneously. On the other hand, given that they pass easily through the blood-brain barrier, concentrations achieved in CNS doubles those that are quantified in the peripheral circulation. They also cross the placental barrier, reaching to the fetus during pregnancy. Due to their lipophilic properties, antipsychotics are stored in the peripheral fat, so dialysis is ineffective in cases of overdose. Traditional antipsychotic drugs are metabolized

in the liver via hydroxylation and demethylation in cytochrome P450 processes. Some, such as haloperidol, suffer an additional glucuronidation and remain active as dopamine antagonists. Major isozymes in the metabolism of these drugs are the 2D6 and the 3A4. It is estimated that between 5 and 10% of individuals in white, and one much higher proportion of black individuals are slow track metabolizers of cytochrome P450 2D6, so it is predictable that submit side effects with a greater frequency and severity. The AP are removed primarily by urine and feces, through bile, but also by the saliva, tears, sweat, and breast milk. The elimination half-life varies between 18 and 40 hours. In the elderly, who often have impaired kidney function to a greater or lesser extent, physician should proportionally reduce the dose.

Atypical or Second-Generation Antipsychotics (SGA)

Clozapine produces a total blockade of D2 receptors, so it does not cause extrapyramidal symptoms. Properties of clozapine are due to the combination of a low affinity for the D2 receptors along with strong affinity to serotonergic 5HT2A and 5HT1C, adrenergic and cholinergic receptors. Clozapine joins less intensely this receiver, which is displaced by endogenous dopamine. This property is present in many SGA, not only clozapine, so these drugs cause fewer movement disorders as side effects. The indication of clozapine is the treatment of schizophrenia in patients who do not respond (after at least two months of treatment at appropriate doses) or that they do not tolerate the AP, although occasionally prescribed for other purposes such as the treatment of psychosis by L-DOPA in Parkinson's disease patients with mania. It can produce leukopenia, so it's important to control it weekly during the first six months of treatment and every fifteen days from then. However, it should be noted that this risk is low, less than 1%. Other adverse effects are orthostatic hypotension and tachycardia, increased sedation, and the decline of the seizure threshold with the consequent risk of convulsions in 5-10% of cases. Some patients develop a symptomatic complex called metabolic syndrome which consists of weight gain, increased insulin resistance, increased risk of diabetes type 2, and elevation of plasma lipids. Clozapine may increase plasma levels of enzymes such as transaminases GOT and GPT (alanine aminotransferase and aspartate aminotransferase), alkaline phosphatase, gamma glutamyltranspeptidase (GGT) and lactate dehydrogenase.

Risperidone

Its mechanism of action is mediated by its high affinity for D₂ receptors, 5HT_{2A} receptors and the adrenergic α_1 and α_2 receptors. Unlike haloperidol shows a low affinity for muscarinic receptors for which leads to fewer anticholinergic effects. With a similar effectiveness or even something greater than haloperidol, involves a greater tolerance, although risperidone at high doses can also cause extrapyramidal symptoms. It is considered an SGA first line in the treatment of psychoses with particular effectiveness in

the prevention of recurrences. It has been used in child psychiatry in the treatment of aggressive and serious behavior disorders. There is an increase in brain-vascular accidents in connection with the use of risperidone and olanzapine in elderly patients with dementia, a complication which advised the prescription of this drug with much caution in such patients. There is a long-acting form of risperidone that can be used twice a month in injection for maintenance treatment.

Olanzapine

Its main indication has been the treatment of schizophrenia, acute episodes of mania and maintenance of bipolar affective disorder. Its structure is similar to clozapine and its mechanism of action is unknown, although it has a stronger affinity for the receptor 5HT_{2A} than by the dopamine receptor D₂. Olanzapine also acts at various levels, interacting with D₁ and D₂ dopaminergic, 5HT_{2A} serotonergic, H1 histaminergic, and muscarinic receptors. Among his include anorexia nervosa, post-traumatic stress disorder and borderline personality disorder where, at low doses, it seems to improve objectives such as aggression and impulsiveness parameters. Olanzapine is metabolized in the liver by oxidation and glucuronidation by cytochrome P450 isoenzyme 1A₂. In smokers it must be important to adjust the dose, since the consumption of cigarettes induce 1A₂ isozyme and increases drug elimination. The main adverse effect that occurs in patients in treatment with olanzapine is weight gain, so, an important risk that must be considered in relation to this and other drugs which produce significant weight gain is the metabolic syndrome. Other side effects of olanzapine are: sedation, elevation of prolactin, leukopenia (without agranulocytosis), and decrease the seizure threshold. Olanzapine carries a lower risk of episodes of Parkinsonism, dystonia and tardive dyskinesia.

Quetiapine

It has clozapine similar profile, with a moderate affinity to D₂ receptors and moderate-intense to 5HT₂ serotonergic receptors. It is a partial agonist of 5HT_{1A} receptors, which increase dopamine concentrations in mesocortical area, improving cognitive and negative schizophrenics symptoms. It produces few extrapyramidal symptoms and risk of tardive dyskinesia. These features make it the choice for the treatment of disorders of behavior in Parkinson's patients and patients treated within the framework of liaison psychiatry. Undesirable side effects are sedation and weight gain with alteration of glucose and lipid metabolism. However, it does not produce a significant increase in prolactin levels. Quetiapine is metabolized in the liver by the cytochrome P450 3A4 enzyme, so drugs that produce a large inhibition of the isozyme (such as erythromycin) may increase their serum levels. Carbamazepine and phenytoin reduce levels of quetiapine as behave as enzyme inducers forcing adjust the dose to avoid possible relapse in patients who are simultaneously being treated with these drugs.

Ziprasidone

It has high antagonism of 5HT_{2A}, 5HT_{1D}, 5HT_{2C} serotonergic and D₂ dopaminergic receptors. It has a low tendency to cause extrapyramidal effects because them high ratio 5HT_{2A} / D₂ and its low affinity for adrenergic, muscarinic and histaminergic receptors. Ziprasidone is metabolized in the liver by isoenzymes 3A4 of the P450, through a process of reduction effect of aldehyde oxidase. Its bioavailability increases when ziprasidone is administrated along with food. This compound intensely joins proteins and has not been shown to see displaced by other drugs with similar affinity. In addition to the indication in the acute treatment and maintenance of schizophrenia, given that it exists in injectable presentation, you can use in patients who do not collaborate in the taking of oral medication and in emergency situations characterized by agitation or serious behavior disorders. It is the antipsychotic with a lesser influence upon weight. The most frequent adverse effects are drowsiness, insomnia, constipation and nausea. Normally these effects tend to be temporary and, in general, ziprasidone is well tolerated.

Amisulpiride

While it has no affinity for subtypes D₁, D₄ and D₅ presents affinity on the D₂ and D₃ of the dopamine receptor subtypes. Unlike other AP, it has no affinity for serotonergic, adrenergic, cholinergic and H1 histaminergic receptors. An important feature that distinguishes it from other antipsychotic group is its low liver metabolism which must be taken into account within the framework of the psychiatric consultations when treating patients with liver failure that you do not need to adjust the dose. Their degree of plasma protein binding is low (around 16%). The drug is eliminated through the kidneys in 90% during the first 24 hours. In patients with severe kidney disease dosages should be reduced.

Aripiprazol

This is a partial agonist of dopamine receptor D₂, D₃ and serotonergic 5HT_{1A} and works as a 5HT_{2A} serotonin receptor antagonist. In some situations, aripiprazole would act as an antagonist and in others as agonist. That way there would be a self-regulation of dopamine, so the drug would act as antidopamine at the mesolimbic via and as prodopamine at the mesocortical via, without significantly affecting the nigrostriada or the tuberoinfundibular paths. Its theoretical advantages would be improvement in cognitive aspects and motor effects in the long term such as tardive dyskinesia. It is metabolized in the liver by isoenzymes of the cytochrome P450 3A4, and 2D6 so that compounds which interact at this level (carbamazepine, quinidine, ketoconazole, fluoxetine and paroxetine) could alter the plasma concentrations of aripiprazole. It is a well-tolerated drug that does not affect significantly the weight or the levels of prolactin for patients, or metabolism of glucose and lipids. The most frequent side effect is drowsiness.

Paliperidone

It is an active metabolite of risperidone. It presents a great affinity for 5HT_{2A} receptors and moderated by the D₂ receptors, with a lower lipophilicity than risperidone. The pharmacological activity of this compound is similar to another high-power SGA. The receptor binding profile is similar to risperidone and ziprasidone, though unlike risperidone and another SGA it has a low rate of hepatic metabolism. Its adverse effects are similar to the risperidone although they produce a greater increase in the rate of hyperprolactinemia [5].

Benzodiazepines

Benzodiazepines (BZD) are CNS depressors with anxiolytic and hypnotic-sedative properties, and antiepileptic and muscle relaxing effects. They are more secure in overdoses than barbiturates and other sedative drugs. They have similar action mechanism and side effects, and differ in onset time and activity duration, which is relevant in treatment and indications. Absorption in the gastrointestinal tract is very good, especially on an empty stomach, so that the oral via is the choice for these agents. Diazepam and clorazepate are absorbed more quickly than the others. Other routes of administration are less recommended and should be reserved only for cases of urgency: the intramuscular absorption is erratic and intravenous absorption can be dangerous. The BZD are lipophilic agents, so cross the blood-brain barrier well, exerting their action at the level of the central nervous system quickly. They also cross the placental barrier and are excreted through breast milk. Furthermore, their solubility makes that most of them are accumulated, gradually, in body fat resulting in a high volume of distribution, which directly influences the duration of the action. The biotransformation is at hepatic level through a process of oxidation and conjugation. Some BZD (such as the diazepam or clorazepate) have pharmacologically active metabolites which, sometimes, even have longer life than the active ingredient. In addition, should consider that in the healthy elderly these processes are altered, so you have to choose BZD not metabolized by microsomal liver enzymes and without active metabolites as oxazepam or lorazepam. They are eliminated on a majority basis through the kidneys (70-90%), after their hepatic metabolism. The rest are eliminated through the stool or bile. All BZD's action is at CNS, by their ability to enhance the inhibitory actions of GABA, stimulating the GABA-A receptor. It is believed that their anxiolytic action is due to the inhibitory action on neurons in the limbic system, including the amygdala, and serotonergic and noradrenergic neurons of the CNS. The fact that ethanol, barbiturates, and BZD have similar actions on the same receptor explains their drug synergy (and therefore the danger of the combined overdose) and its cross tolerance. This last property is used in the detoxification of alcoholics with BZD [6].

Drugs used in opioid addiction: Methadone

Methadone is an opioid analgesic with an outstanding action on

the mu receptor. In cases of opioid dependence methadone is useful for treatment of detoxification, maintenance, and harm reduction.

Special situations

Opioid analgesics are generally contraindicated in acute respiratory depression, obstructive respiratory processes and patients in treatment with opioid antagonists (naltrexone). They are also contraindicated or should be used with great caution in alcoholism, seizure disorders, head injuries and processes that have increased intracranial pressure. They must not be administered to patients in a coma. In patients with biliary disorders it's usually recommended to avoid the use of opiates. Opioid analgesics should be administered with caution or dosage reduced in patients with: hypothyroidism, adrenocortical insufficiency, asthma, or decreased respiratory reserve, kidney or liver failure, prostate hyperplasia, hypotension, shock, inflammatory or obstructive intestinal disorders and myasthenia gravis. The dose should be reduced in elderly or debilitated patients. Methadone can prolong cardiac QT interval, increasing the risk of torsades de pointes, which implies risk of sudden death.

Renal failure and psychoactive drugs

If the drug is dialyzable, such as lithium, it will experience a sharp decline in its blood levels after dialysis, so post-dialytic of such drugs levels should be obtained to determine what amount is provided after the process. Certain drugs that are metabolized / eliminated by the kidney will accumulate, with the risk of toxicity, despite not using high doses of these, so that such drugs should be avoided or give at lower doses. In general, the doses to be used will be two-thirds of the usual doses of the drug, except drugs with primarily renal elimination, in which will have to evaluate the clearance of creatinine (ClCr) as an indicator of renal function and the dose to use of the drug. Plasma levels of the drug in question must be controlled, at least once a month, and immediately after the initial dose of medication must provide wherever possible. In renal failure protein binding is lower than in healthy individuals, so usually there is a greater amount of free drug in plasma, with higher therapeutic and side effects. The higher protein binding, the lesser dialyzable is the drug, what it's important to prescribe lower doses. In general, most of the psychotropic substances aren't dialyzable, except lithium, gabapentine, pregabalin and others [7].

Conclusion

Psychiatric medicines have changed the lives of people with mental illnesses for the better and many people have gone on to live fulfilling lives with the help of these medicines. Today, there is a wide range of safe and effective medicines available to treat these illnesses and it is important to know the medicines that your doctor prescribes to you. Besides knowing what they are and what symptoms they treat, it is good to be aware of some of the side effects so that you would be able to talk to your doctor about

them. Adhering to medication dosages and schedules is important. If you wish to adjust the medication routine, please consult your doctor as abruptly stopping some of these medicines may cause a Discontinuation Syndrome, with either a worsening of earlier symptoms or the appearance of other physical or psychological symptoms.

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