

Derlemeler/Reviews

Psychopharmacological Treatment of Depression

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ABSTRACT:

PSYCHOPHARMACOLOGICAL TREATMENT OF DEPRESSION

Correct diagnosis, cooperation of the patient, right dosage and the observation of the efficacy of the drug on the therapeutic improvement of the patient are always good means in reaching a successive treatment. As well as it is important for the clinician to have a precise knowledge of the disorder, it is as important for him to acquire the knowledge on advantage, disadvantage and the mechanism of the action of the drug he uses and the strategies for medication utilisation as well. In this article, pharmacokinetic properties, side effects, interaction and associative properties of classic and new antidepressants are reviewed and the antidepressant prescription rules are summarised with the light of these reviewed data.

Key words: depression, drug treatment, antidepressant

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ÖZET:

DEPRESYONUN PSİKOFARMAKOLOJİK TEDAVİSİ

Depresyonun farmakolojik tedavisinde doğru tanı, hastanın tedaviyi kabulü, seçilen ilacın uygun dozda kullanılması ve hastanın sonraki takip muayenelerinde kullandığı ilacın iyileştirici etkinliğinin objektif bir şekilde görülmesi; tedavinin başarıya erişmesi için izlenecek iyi bir yoldur. Tedaviyi uygulayan klinisyenin yeterli bir düzeyde hastalık bilgisine sahip olması yanında; hastası için seçeceği ilacın avantaj, dezavantaj ve etkileşim mekanizmalarını içeren ürün bilgisini edinmiş olması ve ilaç düzenleme stratejilerini iyi bilmesi gerekir. Bu yazıda klasik ve yeni kuşak antidepressif ilaçların farmakokinetik özellikleri, yan etkileri, etkileşim ve eşkullanım özellikleri gözden geçirilmiş ve değerlendirilen bilgiler ışığında antidepressanları reçete etme kuralları özetlenmiştir.

Anahtar sözcükler: depresyon, ilaç tedavisi, antidepressan

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An attentive clinical assessment may often permit to distinguish the major depressive episodes from an isolated depressive symptom requiring anti-depressant treatment (often transient), that doesn't justify medicinal treatment (e.g. mourning).

The use of medicines is only justified:

1) if the diagnosis of the depressive episode is confirmed by a collection of clinical assessments (low self-esteem, guilt, slower psychomotor activity, anxiety, weight loss, sleep interruption...).

2) if it is possible to obtain with the co-operation of the patient for an adequate dosage, an assessment of 4 to 8 weeks necessary for the development of full efficacy.

3) if a regular check-up of the patient occurs for the assessment of the therapeutic benefits and whether it is of interest to pursue or not the treatment during the phase of convalescents (4 months after the remission of symptoms).

The patient may require emergency measures: hospitalisation, electroshock, e.g. due to suicidal risks.

Two pitfalls must be avoided:

- the unnecessary prescription to each patient presenting manifestations of asthenia or the pseudo-depressive states,

- the non-utilisation of antidepressant medicine while prescribing anxiolytics, as far from improving the situation, risks the likelihood of aggravating the disorder.

If the correct product is chosen and adhered to one observes 70% efficacy.

The prescription of an antidepressant therefore requires:

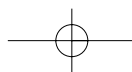
- the precise knowledge of the illness
- the knowledge of the product (advantages, disadvantage, supposed mechanisms of action)
- the knowledge of the strategy of utilisation and association with anxiolytics or sedatives, which is less often considered

I - TRICYCLIC ANTIDEPRESSANTS

In 1950, in search of new antihistaminic mole-

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cules, chemists at the GEIGY laboratory in Bâle, synthesised the molecule imipramine, having a similar structure to the antihistaminic phenothiazines. It failed the first antihistaminic pharmacological tests and the product was set aside and forgotten.

In 1952, the discovery of the multiple actions of chlorpromazine; immediately sent the pharmaceutical industry into a spin and every business wanted to have its own "neuroleptic", but the SPECIA patents were taken and it was difficult to copy the chlorpromazine molecule. The existence of imipramine was then remembered at the GEIGY laboratory and it underwent new pharmacological tests only to reveal again its neuroleptic inactivity. GEIGY persisted in their search and confided in the assistance of a psychiatrist (Kuhn) who prescribed imipramine in the same situations requiring chlorpromazine prescription, but he also found it lacked neuroleptic activity. Here we admire the clinician's persistence, as having noticed certain behavioural changes in patients, retried the molecule in different situations and was the first in 1957 to describe the antidepressant attributes of a chemical substance. (1)

These clinical results were confirmed in Canada in 1959. Psychiatrists spoke of a chlorpromazine-like medicine having a special effect on mood that they qualified as thymoanaleptic.

The term thymoanaleptic defined by Delay represents the main effect of these products; stimulate the mood when it is depressed, while not affecting vigilance, specifically addressing depressive mood. In a patient suffering from depression, antidepressants can surpass their goal and provoke an inversion of mood, either a simple euphoria or sometimes a real manic episode that requires an immediate withdrawal of treatment.

This inversion of mood is more frequent if the patient presented some manic episodes beforehand (bipolar depression). Therapeutic activity only appears after a minimum of 10 to 20 days of treatment and the secondary effects are numerous.

1.1. HYPOTHESES OF ACTION ON THE CENTRAL NERVOUS SYSTEM

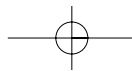
The mechanism of action of the most frequently prescribed anti-depressants is the inhibition of monoamine reuptake, i.e. noradrenaline, serotonin or dopamine. One also observes for the majority of

antidepressants, a reduction of the degradation of these amines, a blockade of the inhibitory feedback, an action at the second messenger level (probably the common action of much antidepressants) as well as post-synaptic action. It was believed for a long time that the common effect of all anti-depressants was "down-regulation", i.e. the reduction of the number of the central beta receptors during chronic administration of anti-depressants, since this disrupts down-regulation or appears about fifteen days after the beginning of administration. (2) It was suggested as a rational explanation as to the activity of antidepressants, as the clinical effects were not manifested until after this time had elapsed. Unfortunately, it has since been uncovered that antidepressants down-regulate more than just the beta adrenergic receptors, as the newer antidepressants are clinically active through the inhibition of the serotonin reuptake. Even through the down-regulation of the beta-receptors is observed with fluvoxamine, fluoxetine and sertraline; this is not the case with citalopram and paroxetine, however all SSRIs normalise the function and density of the 5-HT₁ and 5-HT₂ receptors (see further on). Thus, one supposes that the common action of antidepressants can be associated with the down-regulation of the serotonergic receptors. Antidepressants may serve as mediators between the noradrenergic and serotonergic systems. Many hypotheses have recently been formulated. Indeed, animal studies have shown that tricyclic antidepressants can themselves interact with G-proteins. (3)

1.2. PHARMACOKINETICS OF TRICYCLIC ANTI-DEPRESSANTS

The pharmacokinetics of tricyclics are characterised by:

- a generally long resorption (4-8 hrs.) partly due to a parasympatholytic effect that slows down gastric drainage
- a first pass metabolism effect of 40 to 70% depending on the tricyclic derivative
- a strong percentage binding of plasma protein with important inter-individual fluctuations for the liberated fraction, that may be pharmacologically active
- a principal hepatic elimination with enterohepatic cycles conferring the anti-depressants with long half-lives with notable differences among individuals



and medicinal interactions

- a variable plasma equilibrium state between subjects due to the inter-individual variations of plasma clearance (300 to 1200 ml/min.).

- at the end of 1-4 weeks a functional balanced concentration state is achieved between the antidepressant and metabolite (which may be more or less active).

- they rapidly distribute quickly to all tissues and their peripheral action appears 1/2 hour after ingestion.

- they undergo several transformations, in particular a monodesmethylation; in some cases the monodesmethyl derivative may then be more active than the dimethyl product. Other transformations include N-oxidation, hydroxylation followed by glycoconjugation leading to urine metabolite elimination: 40% of the dose is eliminated in the urine in 3 days (\neq with M.A.O Is.), half-life of 30hrs and achieving an equilibrium state in 5-8 days. (4)

In humans the principal antidepressant or sedative effect is dependent on the proportion of the N-desmethyl metabolite formed, however this desmethylation not only presents important individual differences from one individual to another, but also in the same individual as a function of time e.g. the desmethyl derivative of maprotiline is inactive. (5)

Plasma product and derivative concentrations.

It is necessary to verify plasma concentrations in case of therapeutic failure or to eliminate an atypical metabolite: too weak/strong desmethylation.

1.3. SIDE EFFECTS AND TOXICOLOGY

1.3.1 - Provoked by massive ingestion of strong doses (suicide)

Cardiovascular toxicity of tricyclics is a major element: it is a dramatic and irreversible toxicity with:

- contraction disorders impairing left ventricular function

- repolarisation disorders, widening the QRS complex on ECG resulting in circulation problems, particularly cerebral, of anoxic convulsion origins.

It is a serious and relatively frequent poisoning (the risk of suicide being very high in patients receiving this kind of treatment) and poses a problem for the emergency services in the resuscitation of this type of intoxication. Indeed, the toxicity is irreversible and the only efficient gesture is to prevent

the resorption of the poison (pumping of the stomach) or symptomatic treatment and sodium lactate perfusion and monitoring, reducing the death rate. (6)

1.3.2 - Provoked by therapeutic doses

The individual's response to these medicines varies from one patient to another.

4 types of incidents or accidents have been described.

a) Those associated with the nature of the treated illness

It is the inherent suicidal risk of the treated illness which is at its worst after a few days of anti-depressant treatment (inversion of mood). Motor disinhibition occurs prior to the disappearance of the psychiatric syndrome: suicide

Co-prescription with Tercian® (cyamemazine) is recommended, the association with benzodiazepines is controversial due to disinhibition. The inversion of mood and the appearance of a manic state is especially dangerous in ambulatory cases. Delirium may appear in psychotic patients.

b) Side effects linked to the central nervous system

The neurological manifestations are relatively frequent but nevertheless less impressive than those of neuroleptics:

- different types of tremors (1/3 of cases):

- . subtle tremors of the tongue and hands (emotional type)

- . slow tremors at rest but without muscular hypertonia

- . frequent dysarthria

- . the "dysarthria-tremor" syndrome often disappears with a reduction of dosage

- some convulsions may occur at the beginning of treatment in subjects with a previous history of epilepsy (or benzodiazepine withdrawal)

- sleep disturbance is difficult to judge as often the patients suffer from insomnia.

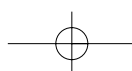
- weight gain, especially for antihistamine molecules such as amitriptyline and maprotiline.

c) Side effects linked to the autonomous nervous system

Problems are mostly due to muscarinic effects.

- dry mouth

- tachycardia and arrhythmia are indicated by an ECG showing quinidine-like effects: prolongation of QT, ECG surveillance is required especially if there is a previous history of cardiovascular problems



- gastrointestinal effects: nausea, sickness and most often constipation, aggravated by phenothiazines or antiparkinson drugs and resulting in a paralytic ileus

- genito-urinary disturbances: retention of urine and dysuria. In the aged male patient, a prominent prostate can trigger an acute retention of urine

- there is also a reduction of libido and erection loss

- ophthalmic adaptation mydriasis and paralysis are also due to anticholinergic action and closed angle glaucoma is a definite contra-indication

- hypotension associated with an action on the sympathetic system is frequent (alpha adrenergic blockade)

- night sweats are abundant, accompanied by hot flushes.

1.3.3 - INCIDENTS AND ACCIDENTS DUE TO ASSOCIATIONS

- definite contra-indications of association with the M.A.O.s

- often in the case of polymedication with other psychotropics, the relation between plasma concentration and dosage is impossible to determine.

II - PHARMACOLOGICAL PROPERTIES OF ATYPICAL ANTIDEPRESSANTS (NON-MAOI - NON-TRICYCLIC) (5)

1. Mianserin (ATHYMIL®) a piperazozepine, possesses a tetracyclic structure. It doesn't modify the reuptake of the different amines; on the other hand, it increases the turn-over of noradrenaline without affecting those of serotonin and dopamine. It blocks presynaptic alpha 1 action. Pharmacological studies in animals show that mianserin antagonises the action of serotonin in many tissues, notably at the level of the blood vessels. It also possesses anti-histamine properties as well as a sedative action, probably due to its alpha antagonistic effect. Its central or peripheral anticholinergic effect is modest.

2. Tianeptine (STABLON®) possesses an effect on mood disorders categorising it between the sedative and stimulant antidepressants. After a rapid and complete resorption its distribution is associated with a high protein binding (close to 94%). Hepatic metabolism occurs by beta-oxidation and N-desmethylation.

3. Viloxazine (VIVALAN®) is a compound whose structure is similar to that of propranolol which is a beta-blocker, however, viloxazine lacks propranolol's properties. Even though viloxazine has a different structure to the tricyclics, it possesses many pharmacological analogies with these derivatives. It is a weak enough inhibitor of noradrenaline reuptake, it may possess an indirect beta-mimetic action.

Its central and peripheral anticholinergic activity is weaker than that of tricyclics and it causes a moderate and transient concentration increase of the cerebral biogenic amines.

III - MONOAMINE OXYDASE INHIBITORS

For the pharmaceutical industry, the aim was to create new molecules differing from the old MAOIs in at least two fundamental points: the selectivity (either for MAO-A or MAO-B) and the reversibility of the link associated to enzymatic inhibition. One distinguishes 2 types of MAOIs:

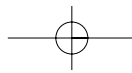
1) NON-SELECTIVE MAOIs

These are the older irreversible types represented by nialamide and iproniazide. Their efficacy is comparable to that of the reference tricyclic antidepressants but they are never prescribed to begin with due to the fact of their difficult handling management. These products are reserved for depressive states resistant to tricyclic antidepressants; in fact they are rarely prescribed.

The side effects are essentially linked to the blockade of catecholamine degradation (notably peripheral): orthostatic hypotensions are frequent, sudden hypertension has been described, notably in cases of ingestion of food containing tyramine (cheese effect).(7) A delay of fifteen days is required in cases of general anaesthesia.

2) MAOI-As

These are specific inhibitors of monoamine oxidase A. Food and medicinal interactions are considerably reduced optimising the handling and tolerance to these new MAOIs, principally toloxatone (HUMORYL®) moclobemide (MOCLAMINE®) and befloxatone. The pharmacovigilance of these products confirms their good acceptability at therapeutic doses.



IV – SPECIFIC SEROTONIN REUPTAKE INHIBITORS (SSRIs)

These serotonergic antidepressants are well developed due to their close efficacy to the tricyclics but with weak anticholinergic effects and absence of cardiac toxicity. They are prescribed in disorders other than depression (panic disorder, obsessive compulsive disorder etc.).

1. INDICATIONS

For the major DSMIV depressive states the SSRIs are the most prescribed anti-depressants. Their first preference utilisation is easily justifiable for poly-medicated patients, suffering cardiovascular pathologies.

- Fluoxetine (PROZAC®): Its oral resorption is good, bioavailability varies from 70-85% and it is not modified by foods. Its half-life varies from 1-4 days and that of its metabolite, norfluoxetine, is of 7 days. Fluoxetine is prescribed at a dose of 20 mg/day.

- Sertraline (ZOLOFT®): possesses a half-life of around 24 hrs which allows a once daily dosage. The bioavailability is 88%. Binding to plasma proteins is 99%. Sertraline is metabolised by the cytochrome P450 iso-enzymes and results in the metabolite: desmethylsertraline, possessing little active. Sertraline is prescribed at a dose of 50 mg/day.

- Paroxetine (DEROXAT®): possesses a half-life of on average 24 hours, binding to plasma proteins is high (95%). Metabolism results in 5 metabolites that are all inactive. Paroxetine is prescribed at a dose of 20-40 mg/day.

- Citalopram (SEROPRAM®): has an excellent bioavailability approaching 100%. Its half life is 33 hours. The binding to plasma proteins is 50%. The main metabolite of citalopram is norcitalopram.

- Fluvoxamine (FLOXYFRAL®): has a half-life of around 16hrs. Its bioavailability is independent of food intake.

2. SIDE EFFECTS

They most often concern the digestive system, with nausea, vomiting and to a lesser degree constipation and anorexia. Insomnia has been described as well as headaches, occasional hyper-perspiration and decrease of the libido. Withdrawal syndromes

have been described due to dosage decrease during the secession of the treatment.

The serotonergic syndrome, often unrecognised, justifies the immediate withdrawal of the treatment. It is due to certain overdoses or interactions and can lead to hospitalisation or even death. (8) A whole order of symptoms are associated with the digestive system (diarrhoea), parasympathetic system (sweats, thermal dysregulation, hypo- or hypertension), motors symptoms (myoclonia, tremors) and neuropsychiatric symptoms (confusion, agitation or even coma).

3. INTERACTIONS

SSRIs can interact with concomitant medication prescription due to the following mechanisms:

Enzymatic hepatic inhibition: explaining the risk of interaction with tricyclic antidepressants, anticonvulsants (carbamazepine and valproic acid), antipsychotics and oral anticoagulants.

Association with other serotonergic products may risk serotonergic syndrome. Also association with MAOIs (even selective) and clomipramine is strongly contra-indicated. (8)

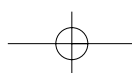
Electrolytic modifications: the SSRIs are susceptible to cause a hyponatremia and the concomitant administration of diuretics increases this risk (care is required when treating elderly patients).

The SSRIs, even though slightly less active than tricyclic antidepressants in clinical studies, have proven to be sufficiently efficient to be used in preference in most depression cases, however their efficacy has not yet been proven in elderly patients over 75 years old.

V – NEW ANTIDEPRESSANTS

Also called dual-action antidepressants, due to the fact of their multiple synaptic impacts.(9)

1. Venlafaxine (EFFEXOR®): this molecule simultaneously inhibits serotonin and noradrenaline reuptake. The metabolism of venlafaxine results in the active metabolite (O-desmethyl-venlafaxine) and two inactive metabolites. It lacks cholinergic or histaminergic receptor activity. Its side effects are similar to those of the SSRIs. There exists a dose-relation response i.e. while increasing the dose one increases



the number of responses.

2. Mirtazapine (NORSET®): this molecule acts simultaneously on noradrenergic and serotonergic receptors. It directly potentialises noradrenergic transmission while blocking central alpha-2 receptors and increasing serotonergic transmission, mediated by 5-HT1 receptors while blocking 5-HT2 and 5-HT3 receptors.(10)

Due to its particular pharmacological profile mirtazapine lacks anticholinergic-, adrenergic- and serotonergic-type side effects. The typically serotonergic side effects such as nausea, vomiting, diarrhoea and sleep interruption were less described in groups treated by mirtazapine and they don't have any consequences on the vital prognosis of patients, even the most aged. Some arthrosis-like side effects can occur but disappear after treatment withdrawal.

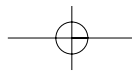
3. Milnacipran (IXEL®): is a serotonin and noradrenaline reuptake inhibitor. The bioavailability of milnacipran is 85%, not modified by food intake. The half-life is short: 8 hrs and plasma protein binding is weak. Metabolism is hepatic and doesn't result in active metabolites. When prescribed in the adult, for major depressive states, milnacipran is used at a dose of 100 mg/day (50 mg twice daily). The side effects seen during clinical studies have only rarely resulted in the withdrawal of treatment. Dizziness, hot flushes and hyper-perspiration, vomiting, nausea and digestive-type signs have been reported. Less frequently reported are dry mouth and constipation. In exceptional cases a serotonergic syndrome may occur and this risk is augmented by the association of MAOIs. The observed overdoses never resulted in death. No cardiotoxicity has been observed.

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VI - RULES OF PRESCRIBING ANTIDEPRESSANT MEDICINES

1. around 30% of depressive states resist chemotherapy,
 2. the prescription of an anti-depressant is only an element of the global therapeutic treatment (+ understanding and quality psychotherapy support),
 3. all depressive state types can benefit from chemotherapy,
 4. the tricyclics dominate in term of absolute efficacy,
 5. three criteria guide the choice of an anti-depressant
 - the severity and semiologic aspect of the depression
 - age and the somatic state of the patient
 - prescription habits of the physician
 6. an anti-depressant cure requires
 - an optimum dosage (150 mg/day for the tricyclics)
 - surveillance and secondary effect correction
 - association of non-systematic psychotropics
 - length of the treatment: at least 6 months for the first episode, 12 months for the second, ten months and more for beyond.
 7. to respect contra-indications
 - due to parasympathetic effects: closed angle glaucoma, prostate hypertrophy, cardiac insufficiency: history of cardiovascular problems heart attack, rhythm problems, coronary inflammation for tricyclics
 - MAOIs association: SSRIs
- Ambulatory treatment
- the mismanagement of the suicidal risk
 - prudence in the progressive increase of doses and frequent consultations. Not to prescribe large quantities of the medicine.



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