Universidade de Lisboa

Faculdade de Farmácia

Racional terapêutico na escolha de antidepressivos: como maximizar a relação benefício-risco?

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Monografia orientada pelo Professor Doutor João Pedro Fidalgo Rocha, Professor Auxiliar

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Therapeutic rationale in antidepressants' choice: how to maximize the benefit-risk ratio?

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Resumo

Com a prevalência de patologias do foro psicológico a crescer exponencialmente nas ultimas décadas, uma abordagem mais eficaz à saúde mental tem-se tornado essencial. Os transtornos depressivos são atualmente a maior causa de perda de saúde não fatal. Uma grande parte da população que sofre de distúrbios mentais não tem acesso a cuidados de saúde adequados. Da percentagem de população que tem acesso a terapêutica farmacológica, cerca de um terço é resistente à mesma, e apenas cerca de metade adere à terapêutica.

A evolução na área terapêutica da psiquiatria trouxe alguma inovação, e principalmente progresso na relação benefício-risco dos fármacos. Ainda assim, esta encontra-se aquém das necessidades atuais da população que sofre de doenças mentais. Uma grande parte dos doentes tratados com antidepressivos sofre efeitos adversos gastrointestinais, sexuais, neurológicos, alterações no peso e no sono. Muitos destes efeitos são comuns, tendo um forte impacto sobre a qualidade de vida dos doentes. Também a eficácia dos mesmos é limitada, sendo estimado que apenas 50% dos doentes respondam ao tratamento inicial.

Torna-se assim urgente não só o desenvolvimento e comercialização de novas opções terapêuticas, como também a otimização da utilização do arsenal terapêutico disponível. A presente monografia procura responder à questão: "Como otimizar a relação benefício-risco de antidepressivos?" abordando o estado da arte da terapêutica antidepressiva, e com base numa revisão de recomendações atuais de associações prestigiadas e publicações recentes. Com um foco na individualização da terapêutica, são reunidas as diferentes estratégias terapêuticas para o tratamento da depressão consoante as especificidades de cada população, nomeadamente para adultos, crianças, adolescentes, mulheres no período peri- e pós-natal, na menopausa, e em populações idosas.

A pesquisa realizada tornou ainda evidente a utilidade da testagem farmacogenética para polimorfismos nos citocromos CYP2D6 e CYP2C19 como forma de detetar metabolizadores rápidos ou lentos de antidepressivos, permitindo melhorar os benefícios e reduzir riscos.

Por fim, o papel do farmacêutico e dos serviços farmacêuticos prestados à população são colocados em destaque devido à sua importância na deteção de problemas relacionados com os fármacos, otimização da eficácia e aumento da adesão à terapêutica.

Palavras chave: Antidepressivos, depressão, relação benefício-risco, segurança, eficácia.

Abstract

With the prevalence of mental health disorders rising in the last decade, a more effective approach to addressing mental health is becoming essential. Depressive disorders are the single largest contributor to non-fatal health loss, yet a big percentage of the world's population has low access to adequate mental care. Of those who do have access, about a third are resistant to pharmacological treatment, and about half do not adhere to therapy.

Evolution in the psychiatric therapeutical area brought some innovation throughout the years and with it an improvement of the benefit-risk ratio of medicines. Nonetheless, this relation is still far from the current needs of people suffering from mental disorders. Adverse effects such as sexual dysfunction, weight, sleep, gastrointestinal and neurological disturbances impact the quality of life of many patients taking antidepressants. Efficacy is also limited, with only 50% of patients responding to initial treatment.

It is therefore urgent not only to develop and commercialize new therapeutic options but also to optimize the use of the currently available therapeutic arsenal. The present dissertation aims to answer the question "How to maximize the benefit-risk ratio of antidepressants?", by summarizing antidepressant therapy state of the art and based on a review of current recommendations from prestigious guidelines, as well as other recent publications. Focusing on therapy individualization, best practices for optimizing the use of antidepressants are gathered for specific populations: adults, children and adolescents, women during peri- and post-natal period, menopause, and in the elderly.

The literature review also showed that pharmacogenetic testing for CYP2D6 and CYP2C19 polymorphisms is a promising way of detecting slow and fast drug metabolizers, thus enhancing the benefit and reducing risks.

Finally, the major role of pharmacists and pharmaceutical care providence is highlighted as essential in the management of depression, to detect drug-related problems, and improve adherence and efficacy of therapy.

Keywords: Antidepressants, depression, benefit-risk, safety, efficacy.

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Abbreviations

WHO – World Health Organization

CDC – Center for Disease Control and Prevention

DSM-V - Diagnostic and Statistical Manual of Mental Disorders

ICD - International Classification of Diseases

CBT - Cognitive-behavioral therapy

ECT - Electroconvulsive therapy

NMDA - N-methyl-D-aspartate

GABA - Gamma-aminobutyric acid

MAOI - Monoamine oxidase inhibitor

TCA - Tricyclic antidepressant

SSRI - Selective serotonin reuptake inhibitor

NSNRIs - Non-selective serotonin and norepinephrine reuptake inhibitors

CANMAT – Canadian Network for Mood and Anxiety Treatments

NICE - National Institute for Health and Care Excellence

APA – American Psychological Association

FDA – Food and Drug Administration

CPIC - Clinical Pharmacogenetics Implementation Consortium

PharmGKB - Pharmacogenomics Knowledge Base

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1 Introduction

At the times we're living in, we are watching a rise of consequences caused by the lack of attention that is paid to mental health. As a society, we are just giving the first steps towards fighting the pandemic of mental health disorders.

According to the World Health Organization, "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity". (1) But regardless of the weight this definition gives to mental health, it is still a great challenge to deal with its burden.

Globally, depressive disorders are ranked as the single largest contributor to non-fatal health loss, accounting for 7.5% of all years lost due to disability. (2) Suicide, a dreadful consequence of lack of mental health, is now the third leading cause of death in teenagers and is the cause of eight hundred thousand deaths per year. (3)

A great percentage of people suffering from mental illness do not receive treatment for their disorder at all, with percentages ranging from 35% in high income-countries up to 85% in low-income countries. Almost half of the world's population lives in countries where there is, on average, one psychiatrist for every two hundred thousand people, and even less when it comes to other professionals trained for psychosocial interventions. (4) But the problem isn't just about access: even with available treatment, around one-third of patients with major depressive disorder show inadequate response to antidepressants, being considered "treatment-resistant". (5)

More recently, challenges regarding mental health are increasing given the economic and social consequences of the COVID-19 pandemic. Even though there is little evidence due to the high speed of events, the World Health Organization speculates an increase in loneliness, anxiety, depression, insomnia, self-harm, and suicidal behavior since the beginning of the pandemic. (6) The Center for Disease Control and Prevention (CDC) recently conducted a survey to capture data on the consequences of the pandemic, reaching quite impressive findings. Of the patients surveyed, 56% of young adults reported symptoms of anxiety and/or depressive disorder, a much larger rate than average. Parents, and more specifically women with children, were affected given the challenges of school closures and lack of childcare, showing an increase in anxiety and

depressive disorder. Essential workers were also more likely to report mental health problems during the pandemic, with a rate of suicidal thoughts of 22%. (7) History demonstrated that the mental health impact of disasters such as pandemics outlasts physical impacts, and present data emphasizes the investment that needs to be made on mental illness.

Giving an overview of concepts related to mental health issues, mood disorders are defined as a group of psychiatric illnesses that can at the same time affect one's energy, emotions, and motivation. (8) They occur when there are abnormal feelings of depression, euphoria, or even psychotic features, being mainly subdivided into depressive or anxiety disorders. (9)

Focusing on depression, it is characterized by a decrease in the activity of monoamine neurotransmitters, predominantly norepinephrine, dopamine, and serotonin, in the brain. Low levels of monoamines give rise to the symptoms of dysthymia, anhedonia, lack of motivation, fatigue, insomnia, and cognitive effects. Additionally, there is the presence of elevated cortisol levels due to high stress. Cortisol is responsible for symptoms such as tachycardia, palpitation, and gastrointestinal symptoms. Chronic stress also changes the immune response and causes reduced neuroplasticity, which can have negative long-term effects. (10)

Overall, depressive disorders' hallmarks are feelings of sadness, loss of interest in everyday activities, feelings of low self-worth, guilt, tiredness, and poor concentration. It can substantially impair a person's ability to function at work or school, or even cope with daily life, and can be long-lasting or recurrent.

Depending on the number, type, and severity of symptoms, a depressive episode can be categorized as mild, moderate, or severe. (2) Besides this, depressive disorders can manifest in many ways, being divided into different forms that may develop under specific circumstances.

Major Depressive Disorder (MDD) is the typically called depression, involving symptoms such as depressed mood, loss of interest and enjoyment, and decreased energy.

When depression presents itself chronically and with milder symptoms, the correct term to use is dysthymia. This condition, also called persistent depressive disorder, is

diagnosed when symptoms are present for over two years. It is unfortunately often overlooked and undertreated. (11)

Post-partum depression is the type of depression experienced by women during pregnancy and after delivery, that can bring feelings of extreme sadness, anxiety, and exhaustion, and make it difficult for mothers to provide daily care for themselves and their babies.

In other cases, individuals can experience symptoms of depression only during the winter months, when there is less natural sunlight, a type of depression identified as seasonal affective disorder. This type of depression, typically accompanied by social withdrawal, increased sleep, and weight gain, usually lifts during spring and summer and returns every year. (12)

Besides the referred forms, other clinical features generate subtypes of depression, such as melancholic, catatonic, psychotic, or with anxious distress. Psychotic depression occurs when a person has severe depression plus the clinical feature of psychosis, such as having disturbing delusions or hallucinations. The melancholic subtype of depression is mainly characterized by a decreased reactivity of affect and low mood, alongside the inability to feel pleasure in normally pleasurable activities, feelings of guilt, and even psychomotor disturbance.

A little different from depression, but also worth the mention since it commonly includes symptoms that meet the criteria for depression, bipolar depression has episodes of low moods and extreme high mood episodes. (13)

In its turn, anxiety disorders are a group of illnesses characterized by feelings of anxiety and fear. Within this group, there are different disorders, such as generalized anxiety disorder, panic disorder, phobias, social anxiety disorder, obsessive-compulsive disorder, and post-traumatic stress disorder. Even though the symptoms differ from depressive disorders, the pharmacotherapeutic approach is in many cases similar, with some antidepressants as a first-line choice. (2)

For all of the mentioned mood disorders, there are specific diagnostic criteria and treatment approaches. Regarding depression diagnosis, there are two main classificatory systems: Diagnostic and Statistical Manual of Mental Disorders (DSM-

V) and International Classification of Diseases (ICD), being the first one the most used taxonomy for research purposes. Both of them are based on the identification of symptoms, with at least one of them being low mood or loss of interest or pleasure. (13) The DSM-V system requires at least five out of nine symptoms for a diagnosis of major depression, present for at least two weeks, and also takes into account the severity of those symptoms. (14)

As for available treatment, general recommendations for clinical management of mood disorders include a combination of pharmacological measures with non-pharmacological ones, including different forms of psychotherapy such as cognitive-behavioral therapy (CBT), and in some cases electroconvulsive therapy (ECT). (14)

Mild depression is usually treated with psychoeducation, self-management, psychological treatments, and in some cases pharmacological treatment. When severity is higher, antidepressants have an even more essential role.

Most mood disorders were treated with opioids and amphetamines until the 1950s when the first antidepressants entered the market. They have been widely used ever since for major depression disorder, anxiety disorders, eating disorders, and even neuropathic pain. (15)

The vast majority of antidepressants act on monoaminergic transmission, but more recently, new mechanisms of action have been studied and used, such as targeting N-methyl-D-aspartate (NMDA) receptor, melatonin, or gamma-aminobutyric acid (GABA) brain systems. (13)

Antidepressants are divided into different classes. Cyclic antidepressants were the first ones to be used in clinical practice. Posteriorly, with the rise of second-generation antidepressants came an improvement in safety as they are more specific and selective, having fewer adverse effects. More recently, a new type of antidepressant referred to as rapid-acting antidepressant entered the market, bringing a new way of treating severe cases of depression.

Despite all of these advances, the antidepressant benefit-risk ratio still needs improvement. Efficacy is far from optimal, with rates of response to initial treatment of only 49,6% (16), and suicide ideation likelihood of non-responders increasing from 6%

to 15%. (17) Tolerability is also unsatisfactory, with non-adherence to treatment rates as high as 56%, largely due to the numerous adverse effects associated with antidepressant use. (18)

To achieve a higher benefit-risk ratio for each patient, several factors must be evaluated. From individual clinical features to patient's preferences, managing mood disorders requires multidisciplinary teams that can select and monitor an individualized option for each case. Clinical guidelines have a large role in this, showing standardized recommendations on how to manage mood disorders and optimize treatment.

"How to optimize the benefit-risk ratio of antidepressants?" is the main question to be answered in the present dissertation. Focusing on depressive disorders, the current benefit-risk ratio of antidepressants will be approached, as well as the novel therapies and future perspectives for mood disorders treatment.

Regardless of new therapeutic options on the horizon, optimization of the use of available antidepressants is essential. This dissertation presents an analysis of the best ways to optimize depression management, prioritizing individualization.

Finally, this topic cannot be discussed without referring to the extreme importance of multidisciplinary teams. As healthcare professionals and having a deep knowledge of pharmacology and pharmacotherapy, pharmacists are crucial from the selection to the monitorization of antidepressants' use. The role and potential role of the pharmacist will be approached, mentioning their part in treatment optimization and counseling around depression in outpatient pharmacies' context.

2 State of the Art

2.1 Antidepressants and their benefit-risk ratio

Since the first antidepressants were marketed, great evolution has been made. New mechanisms of action were discovered along with new molecules that allow a better offer for patients with mental disorders.

Antidepressants can be classified in different ways since there is no generally accepted nomenclature. Older and newer antidepressants are a common way to part them into two groups, but other classifications relate to marketing or pharmacologic effects. In this chapter the main characteristics of each antidepressant class will be assessed, as well as their current benefit-risk ratio.

2.1.1 Older or first-generation antidepressants

2.1.1.1 Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs) were the first antidepressants used in clinical practice. They work by inhibiting the MAO enzyme, which catalyzes the oxidative deamination of monoamines. There are two types of MAO enzyme: MAO-A, which primarily deaminates serotonin, melatonin, noradrenaline, and adrenaline, and MAO-B that breaks down phenethylamine and benzylamine. Both forms deaminate dopamine, tyramine, and tryptamine. Their distribution throughout the body is different with MAO-A predominating in peripheral tissues and MAO-B in the brain. Antidepressants can be selective to either of the MAO enzymes and inhibit it reversibly or irreversibly. (19)

MAO-B irreversible inhibitors include selegiline and rasagiline, which have the least potential for adverse effects in this class. Selegiline, however, loses its specificity with the increase of dose to antidepressant effect levels. Reversible MAO-A inhibitors, such as moclobemide, have the advantage of not being associated with interactions with dietary tyramine. (20)

Common adverse effects linked to MAOIs are orthostatic hypotension, weight gain, sexual dysfunction, urinary retention, and serotoninergic syndrome. However, the most

preoccupying problems associated with this class of drugs are hypertensive crises and their danger in overdose.

These serious adverse effects that MAOIs have, alongside the appearance of new antidepressants, led to a decline in their use. However, they have also been considered a "secret weapon" that provides triple reuptake inhibition and can be useful in a specific sub-population of mood disorder patients. (21)

2.1.1.2 Tricyclic Antidepressants

After the appearance of MAOIs, imipramine entered the market as the first tricyclic antidepressant (TCA) used in clinical practice, shortly followed by its metabolite, desipramine. In the 1960s, amitriptyline and nortriptyline were also introduced. (20) TCAs' mechanism of action relies mostly on receptor blockade, inhibiting noradrenaline and serotonin reuptake with different selectivity.

Overall, TCAs have a low therapeutic index, because even though the efficacy is high, they are associated with numerous adverse effects as a result of cholinergic, histaminergic, and alpha-adrenergic receptor antagonism. Characteristic adverse effects include tachycardia and arrhythmia risk, dry mouth, constipation, urinary retention, blurred vision, and orthostatic hypotension. Sexual dysfunction is not well studied but is thought to be similar to newer antidepressants. (15,22) Moreover, they are dangerous in overdose since they affect sodium channels in a quinidine-like manner, which presents problems in patients with suicidal risk. (20)

In general, TCAs offer advantages over MAOI antidepressants, requiring no food restrictions and having less risk of drug-drug interactions, but they have problematic adverse effects in many patients, so their use is being widely replaced by newer antidepressants.

2.1.2 Newer or second-generation antidepressants

2.1.2.1 Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are nowadays the first-line treatment in major depression. They were introduced in the 1980s, and by the early 1990s already accounted for more than half of antidepressant prescriptions globally. (23) This quick

rise was due to their improved tolerability and safety profile when compared to older antidepressants.

Currently, marketed SSRIs include fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram. (20) More recently, vortioxetine entered the market as an SSRI having also serotonin receptor modulating activity. By blocking the action of the serotonin transporter, it has a higher capacity to increase serotonin levels. (24)

In favor of SSRIs are their advantageous tolerability profile, simple dosing strategies, and thus better treatment adherence. They are relatively safe in overdose, have low anticholinergic activity, and minimal cardiovascular effects. Drug interactions are also not a serious problem, except for minimal interactions for fluvoxamine that inhibits CYP1A2. (15)

Apart from depression, SSRIs are used in various other psychiatric indications, such as anxiety disorders, post-traumatic stress, and obsessive-compulsive disorder. (22)
But while these drugs have advantages when compared to conventional antidepressants, there are still several adverse effects that can compromise patients' quality of life. Overall, the most common class' adverse effects are anxiety, sleep disturbances, gastrointestinal discomfort, and sexual effects. There are some strategies to tackle these problems, such as lowering the dose, slowing dose escalation, or temporarily treating the target symptom. For nausea, the use of ondansetron can be helpful, and lorazepam can be temporarily used for insomnia. (15)
There is also evidence for an increase of suicidality in the young population, so these drugs require close monitoring for suicidal ideations, especially in early treatment. (25)

Serotonin syndrome, a condition where excess serotonin activity leads to cognitive changes, fever, and neuromuscular problems, can occur with these drugs, but the risk is higher if combined with other drugs that increase serotonergic activity in the central nervous system.

Sexual side effects, such as decreased libido, difficulties with sexual arousal, erectile dysfunction, delayed ejaculation, painful orgasm, and anorgasmia, are common. This problem often leads to treatment discontinuation and thus needs to be properly managed. (26)

Even though SSRIs have similar effectiveness and safety profiles, they differ in receptor affinity, chemical structure, and pharmacokinetic properties. (20) Therefore, some adverse effects are different within the same class, and the best antidepressant can be chosen according to patients' needs and characteristics.

2.1.2.2 Non-selective serotonin and norepinephrine reuptake inhibitors (NSNRIs)

The non-selective serotonin and norepinephrine reuptake inhibitors (NSNRIs) are a class of antidepressants that act by a dual mode of action, inhibiting both serotonin and noradrenaline receptors and increasing its levels on the brain. This class includes the drugs venlafaxine and duloxetine. Levomilnacipran is also an NSRNI marketed in some countries, yet its use is not approved in Europe. (27) The selectivity of NSRNIs is different from each other, with the degree of norepinephrine blockade varying between them and only occurring with higher doses for venlafaxine. (15,20,28)

Overall, NSNRIs' tolerability profile is similar to SSRIs. (29) They have no function at alpha-1 adrenergic, histamine H1, or muscarinic acetylcholine M1 receptors, which accounts for their low incidence of adverse effects. However, blockade of serotonin receptors leads to adverse effects such as gastrointestinal toxicity, neurological effects, sexual dysfunction, and discontinuation syndrome. Additionally, their noradrenergic activity enhancement can give rise to an increase in blood pressure and heart rate. (15)

Venlafaxine has higher efficacy than SSRIs but is linked to more adverse effects. On the other hand, duloxetine is less associated with adverse effects such as sexual dysfunction. (15) Duloxetine is also effective in the treatment of neuropathic pain and fibromyalgia. (27)

Similarly to SSRIs, NSRNIs were also associated with increased risk of suicide ideation in children and adolescents, thus close monitoring is recommended. (30)

2.1.2.3 Atypical antidepressants

After the introduction of SSRIs and NSNRIs, several antidepressants entered the market, being often fitted in the called "atypical antidepressants" category, which

comprises drugs with different mechanisms of action and properties. This category includes mirtazapine, bupropion, nefazodone and trazodone.

Mirtazapine is a noradrenergic alpha-2 antagonist, very often used for depression and anxiety treatment. Its unique pharmacodynamic profile also includes histaminergic, serotonin 5-HT2, and 5-HT3 receptors blockade. (29) Some evidence indicates that mirtazapine has a faster onset of action when compared to other antidepressants. (31)

As for risks associated with mirtazapine, it induces dry mouth, drowsiness, and sedation in around 25% of patients. Its antihistaminic activity often leads to weight gain. (15) When it comes to sexual side effects, mirtazapine has a lower incidence when compared to other antidepressants, thus making its use advantageous in cases of non-adherence to antidepressants due to sexual dysfunction. (26)

There is a causal association of mirtazapine with bone marrow depression, and although rare, it is recommended that mirtazapine is stopped if any signs of infection with a low white cell count occur. (32)

Bupropion is an atypical antidepressant whose action is believed to be due to norepinephrine reuptake inhibition and dopamine activity enhancement. It does not affect serotonin, acetylcholine, or histamine levels, and does not interact with monoamine oxidase. Its adverse effects are mostly attributed to dopaminergic and adrenergic action, resulting in overstimulation and agitation, nausea, and insomnia. It is not however associated with sexual side effects, weight gain, or an increase in cardiovascular risk. Bupropion for many clinicians is a choice for augmentation therapy in depression. Interestingly, this drug is also approved in the European Union for "aid to smoking-cessation in combination with motivational support in nicotine-dependent patients", even though the responsible mechanism for this action is yet unknown. (33)

Also classified as atypical antidepressants, nefazodone and trazodone are both serotonin antagonists and reuptake inhibitors.

Trazodone's activity is related to its serotonin 5-HT2 receptors antagonism and partially to its weak serotonin reuptake inhibition. (15) It is recommended as second-line treatment in depression, and in depression with sleep disturbances for its ability to

promote sleep. (34) Nefazodone is a derivate of trazodone, with a similar efficacy and safety profile but associated with a lower alpha-1 activity. (35)

These serotonin antagonists and reuptake inhibitors' main advantages include the low potential for causing sexual effects and sleep disturbances. Adverse effects involve nausea, constipation, sedation, dizziness, and headache. Trazodone can also cause orthostatic hypotension given its alpha-1 adrenergic blocking properties. (29) A specific adverse effect related to nefazodone is its hepatotoxicity, which must be taken into account when prescribing this drug. (35)

2.1.3 Efficacy of antidepressants

As seen above, there is a multiplicity of antidepressants with several indications, inside and outside the scope of mood disorders. Newer generation antidepressants were undeniably a big step forward concerning tolerability of antidepressants, but efficacy is still far from optimal.

Having different mechanisms of action, pharmacokinetic and pharmacodynamic profiles, it becomes important to understand antidepressants' differences in both safety and efficacy to understand how the best choice can be made for each patient.

Regarding efficacy, the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines reviewed a number of meta-analyses, all showing that some antidepressants have a modest superiority to depression treatment response. As evidenced in Table 1, escitalopram, mirtazapine, sertraline, venlafaxine, agomelatine, and citalopram show slight superiority when compared to other second-generation antidepressants. (34)

Other studies suggest that of all second-generation antidepressants, escitalopram and sertraline show both the best efficacy and acceptability and might be therefore the best choice for moderate to severe depression. (36)

More recently, a systematic review and network meta-analysis reached similar conclusions, with amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, vortioxetine, and agomelatine showing the highest efficacy. On the other hand,

fluoxetine, fluvoxamine, reboxetine, and trazodone were found the least effective drugs. (37)

All of the above-referred studies assess the efficacy of antidepressants based on symptom improvement, but evidence is still missing when it comes to improvement in overall functioning. (34)

Table 1 Antidepressants with evidence for superior efficacy based on meta-analysis

Antidepressant	Level of Evidence	Comparator Medications
Escitalopram	Level 1	Citalopram, duloxetine, fluoxetine, fluvoxamine, paroxetine
Mirtazapine	Level 1	Duloxetine, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine
Sertraline	Level 1	Duloxetine, fluoxetine, fluvoxamine, paroxetine
Venlafaxine	Level 1	Duloxetine, fluoxetine, fluvoxamine, paroxetine
Agomelatine	Level 2	Fluoxetine, sertraline
Citalopram	Level 2	Paroxetine

From: Kennedy et al, 2016 (34)

2.1.4 Safety of antidepressants

Comparative Tolerability of Second-Generation Antidepressants

As briefly summarized for each class of antidepressants, there are several adverse effects that limit the use of these medicines, impacting patients' adherence to therapy.

Antidepressants are linked to a broad variety of adverse effects, ranging from mild to severe and from common to rare. There is variability of predominance of these effects amongst classes and within class. As well as it is important to know the comparative efficacy of antidepressants, comparative tolerability is essential to choose the best fitting therapy for each patient.

CANMAT constructed a table to describe the different side effects that are common to each antidepressant, as reported in product monographs, shown in Table 2. It is of key

importance to know the comparative profile of antidepressants as patients have different characteristics, and adverse effects for one patient can even be desirable for another.

Table 2 Comparative tolerability of second-generation antidepressants

	Nausea	Constipation	Diarrhea	Dry Mouth	Headaches	Dizziness	Somnolence	Nervousness	Anxiety	Agitation	Insomnia	Fatigue	Sweating	Asthenia	Tremor	Anorexia	Increased Appetite	Weight Gain	Male Sexual Dysfunction
Citalopram	21		8	19				3	3	2		5	11		8	4			9
Escitalopram	15	4	8	7	3	6	4	2	2		8	5	3		2		2	2	10
Fluoxetine	21			10			13	14	12		16		8	9	10	11			2
Fluvoxamine	37	18	6	26	22	15	26	2	2	16	14		11	5	11	15			1
Paroxetine	26	14	11	18	18	13	23	5	5	2	13		11	15	8		1		16
Sertraline[a]	26	8	18	16	20	12	13	3	3	6	16	11	8		11	3	1		16
Desvenlafaxine[b]	22	9		11		13	4	<1	3		9	7	10		2				6
Duloxetine	20	11	8	15		8	7		3		11	8	6		3				10
Levomilnacipran	17	9		10	17	8			2		6		9						11
Milnacipran	12	7		9	10				4		7	3	4		3				
Venlafaxine IR	37	15	8	22	25	19	23	13	6	2	18		12	12	5	11			18
Venlafaxine XR	31	8	8	12	26	20	17	10	2	3	17		14	8	5	8			16
Agomelatine[c]	C	C	C		C	C	C		C		C	C	C						
Bupropion SR[d]	11	7	4	13	28	7	3	5	5	2	8		2	2	3				
Bupropion XL	13	9		26	34	6			5	2	16				3				
Mirtazapine		13		25		7	54							8	7		17	12	
Moclobemide	5	4	2	9	8	5	4	4	3	5	7	3	2	1	5				
Vilazodone[e]	24		29	7	14	8	5				6	3					3	2	5
Vortioxetine[f]	23	4	5	6		5	3				3	3	2						<1

From: Kennedy et al, 2016 (34)

Overall, citalopram, escitalopram, and moclobemide have the least reported adverse events. Fluvoxamine and venlafaxine are the most associated with nausea, whereas headaches are most common with bupropion. Special emphasis is given also to mirtazapine's tendency to cause somnolence effects. These examples illustrate the importance of deeply understanding the comparative safety profile of antidepressants, as this knowledge makes it possible to adapt the treatment to patients' specific needs.

Sexual Dysfunction

As seen above, antidepressants are associated with worrying adverse effects, such as weight gain, anticholinergic, cardiac effects, and even potentially lethal interactions. These effects are more severe and thus receive more attention than milder effects, such as sexual dysfunction. With the rise of second-generation antidepressants prescription, sexual dysfunction is a common adverse effect that must not be overlooked.

Sexual dysfunction is inconsistently and inadequately reported and is often associated with anxiety and depression even when untreated. Regardless of these limitations, a review study estimates them to be present in 30-40% of patients during treatment with antidepressants. (26) Additionally, even though sexual dysfunction usually remises

after drug discontinuation, there is a small risk for post-SSRI sexual dysfunction development which must be considered. (38)

Antidepressant-induced sexual dysfunction has been identified as a leading cause of medication non-adherence and thus needs to be properly screened for and managed. (39)

Sexual adverse effects' symptoms can be related to disruption of sequential aspects of sexual desire, arousal, and orgasm. Drugs acting on the serotoninergic system were shown to negatively affect all of these 3 phases. (39) These effects seem to be dose-related, and slightly more common with SSRIs and SNSRIs than TCAs or atypical antidepressants. Between SSRIs, paroxetine and escitalopram showed the highest risk of sexual dysfunction. (38–40)

Management of these sexual adverse effects requires an individualized approach that takes into account patients' preferences. Sexual function must be assessed frequently, at the beginning of treatment, during, and after treatment cessation. In some cases, there is the development of tolerance, so watchful waiting is an option in moderate cases. If there is no remission of symptoms, the best strategies are lowering the dose, switching, or trying the drug holiday method, always with medical monitoring. (15,38)

Suicidality

In the early 2000s, published evidence unraveled a possible association between the use of antidepressants an increase in suicide ideation and behavior. Several regulatory agencies issued warnings about this risk for young populations that were using antidepressants. The European Medicines Agency published a referral recommending the inclusion of a warning in the product information of SSRIs and NSNRIs, reflecting the increased risk of suicide attempts, suicidal thoughts, and hostility in children and adolescents. (30) Shortly after, antidepressant prescription significantly dropped for youth in many countries, as well as diagnosis of depressive disorders. Antidepressant use in adolescents is estimated to have reduced by 31%. (25)

Within this context, new studies regarding antidepressants induced suicidality rapidly increased. One meta-analysis reported a reduced risk of suicidal ideas or acts in people aged 25 to 64 years. Two other large studies were conducted, one showing no difference

in suicidality in fluoxetine and venlafaxine, and the other showing decrease in suicidal ideation. (34) A more recent meta-analysis, however, revealed a double risk of aggressive behavior and suicidal thoughts in children and adolescents treated with SSRIs and SNRSIs. (41) Another study compared deaths by suicide and suicide attempts in antidepressant clinical trials before and after 2000, and the authors concluded that there was a significant decrease in the studied outcomes. (42) As for evidence of the highest risk classes of antidepressants, large observational studies show no difference between specific drugs or classes. (34)

In summary, there is an increased risk, however small, for suicidal ideation and action in young people that are taking antidepressants, for no class in particular. This risk is higher during the first phase of treatment. Therefore, clinicians must pay attention to early symptoms such as mania, agitation, akathisia, and sleep difficulties, as they can lead to an increased risk for suicidal ideation and behavior. Nonetheless, the benefit of antidepressants for depression treatment clearly outweighs the risks, as the number of youth that benefits from their use is much greater than the number who experience these events.

Close pharmacotherapeutic monitoring is recommended, as well as educating patients and their families to pay attention to alarming adverse effects. Developing a safety plan with the patient and teaching distress tolerance are also effective ways to help to prevent suicidal behavior. (25)

Weight Gain

Weight gain is an adverse effect of most antidepressants, some of which in the first-line treatment for depression. This adverse effect can give rise to several comorbidities, thus representing an important clinical challenge. (43) It may occur both in acute and maintenance treatment phases, and a significant proportion of patients is estimated to be affected.

More than one mechanism may be responsible for antidepressant-induced weight gain. Firstly, antidepressants act on specific neuroreceptors than regulate appetite. Then, symptoms as dry mouth and throat can lead to increased intake of caloric beverages. Finally, there may be a decrease in caloric expenditure due to sedative effects. (44)

Even though there are several antidepressants associated with weight gain, there is significant risk variation between specific medicines and classes. Mirtazapine is the most associated newer generation antidepressant with weight gain, followed by paroxetine.

Nonetheless, some antidepressants are associated with the opposite effects. Bupropion, vortioxetine, and ketamine have minimal effects on weight, and may even induce weight loss. (43,45)

Some antipsychotics are also associated with weight gain. Given the fact that these drugs are used in combination with antidepressants as augmentation therapy in depression treatment, it is important to be mindful of possible risk increase for this adverse effect. (45)

As there are currently no metabolic guidelines for antidepressants, it is important to closely monitor changes in weight in patients who are taking antidepressants. Both the assessment of patients' preferences and monitoring of effects should be prioritized in the pharmacological treatment of mood disorders.

Affective Disturbances

Many people taking antidepressants report emotional feelings like feeling “toned down”, or on a “limbo”, not caring about issues that had importance before. These symptoms characterize emotional blunting, a common adverse effect of antidepressants. This restriction in the range of emotions is however not only an adverse effect of antidepressant use but also a symptom of depression. It is reported by nearly half of patients taking antidepressants as a depression treatment, not only with SSRIs but also mirtazapine, reboxetine, and agomelatine. (46)

Another affective disturbance that occurs usually in the first three months of treatment is an activation syndrome. This is characterized by symptoms of anxiety, panic attacks, irritability, agitation, insomnia, and even aggressiveness. (44)

Other adverse effects

In addition to the covered adverse effects, some antidepressants have an additional risk by being associated with uncommon, yet severe adverse effects.

A substantial body of evidence shows that antidepressants are linked to some cardiovascular adverse effects. Second-generation antidepressants have fewer anticholinergic side effects when compared to older antidepressants as TCAs. (44) Even so, citalopram and escitalopram were associated with prolongation of the corrected QT interval, a surrogate marker for Torsade de Points and other arrhythmias. A comparative study of QT prolongation with SSRIs found that there is only clear evidence of this effect in citalopram and escitalopram, therefore concluding that it is not a class effect. (47) Even though this risk is low, prescribing antidepressants to patients with cardiovascular comorbidities requires caution and careful monitoring of cardiovascular electrocardiogram parameters. (34)

A causal association was found between long-term use of antidepressants and risk of falls and fractures. (48) The use of antidepressants with antagonist alpha-1 receptor activity such as TCAs is well known to cause orthostatic hypotension. This effect is also observed with newer-generation antidepressants in older populations, with paroxetine and fluoxetine show the highest evidence for causing postural hypotension. (44) However, the risk of falls and fractures in the elderly unrelated to postural hypotension was also found in observational studies. (34)

Other evidence shows that the association between depression and greater fall risk may not be completely explained by antidepressant use, as untreated patients also have an increased risk of falls and fractures. (49)

Regardless of the cause, it is important to consider this increase in the risk of falls and fall-related injuries when prescribing to more vulnerable patients.

Antidepressant-induced hyponatremia is a relatively common problem in older adults with other risk factors for hyponatremia, such as the use of diuretics. In these cases, the most appropriate antidepressant seems to be bupropion, since it is not associated with hyponatremia. SSRIs, SNRNs, mirtazapine are not recommended in this subpopulation. (34,50)

Another possible adverse effect to pay attention to is bleeding. SSRIs can inhibit platelet aggregation leading to an increased risk of gastrointestinal bleeding, bleeding in surgeries, and even intracranial bleeding. This risk seems to be higher in patients taking nonsteroidal anti-inflammatory drugs, patients with preexisting platelet dysfunction, or concomitant use of heparin. (44) Concomitant use of acid-suppressing drugs may be necessary to reduce risk in these patients. (51)

2.2 Novel antidepressants and future perspectives

The history of antidepressants undeniably brought a vast and diverse list of available medications for a variety of indications. Despite the clear evolution since the first antidepressant was marketed, clinicians still look down the psychiatric drug pipeline in hope of a breakthrough that will maximize the benefit-risk ratio of antidepressants.

In the past decade, some antidepressants entered the market bringing advantages relative to previously available options. However, antidepressants still have troublesome adverse effects in a great percentage of patients, which makes it important to keep trying to find better alternatives for mood disorders treatment. Fortunately, there are a number of promising agents under development that can ward off the risks associated with conventional antidepressants.

Up until recently, the development of antidepressants was mostly based on trying to increase monoamines' levels in the brain. Given the need for innovative strategies, scientists started focusing on different targets. The glutaminergic pathway is currently one of the newest and most promising pathways to achieve antidepressant effects with higher safety and tolerability.

Studies about ketamine, an N-methyl-d-aspartate (NMDA) receptor antagonist used mostly as an abuse drug in the twentieth century, have been showing its potential with antidepressant fast-acting and long-lasting effects. From this groundbreaking discovery, research started focusing on other NMDA antagonists with less dissociative effects. (52)

In 2019, the European Medicines Agency along with other Health Authorities approved esketamine nasal spray for treatment-resistant depression in adults, in combination with an SSRI or SNRI. (53). Esketamine is the S-enantiomer of ketamine, also acting as an NMDA receptor antagonist influencing glutamate transmission. Its fast onset of action makes it useful for emergencies treatment in patients that have depression and active suicidal ideation. (54). Esketamine's efficacy and safety were investigated in five phase III studies, and the benefits versus risks were assessed in a study that concluded that treatment benefits of esketamine nasal spray plus an antidepressant exceed risks when compared with treatment with antidepressants alone. (5)

Within the same class, hydroxynorketamine is being studied as an alternative to ketamine and esketamine. This ketamine's metabolite is promising for having demonstrated faster antidepressant activity and no dissociative effects. (55)

Similar to ketamine, nitrous oxide (N_2O) is an NMDA receptor inhibitor. Recent evidence indicates that N_2O significantly reduces depressive symptoms in a group of patients with severe treatment-resistant depression. (56) No psychomimetic effects are associated with N_2O use, yet adverse effects such as nausea, anxiety, and headache may represent barriers when assessing therapeutic advantage. (55)

Interestingly, a broad-spectrum antibiotic, D-cycloserine, also showed NMDA glycine receptor partial agonism. It was effective in the maintenance treatment of bipolar depression patients after a single ketamine infusion, making it a promising option in this population. (57)

While GABA neurons represent only fifteen to twenty percent of the total neuronal population when compared to glutamate, their inhibitory effect shows great potential as antidepressant therapy, making these receptors another rising target for antidepressants. (58)

Allopregnanolone is an endogenous neuroactive steroid that acts on the GABA-A receptor and improves symptoms of depression by increasing GABAergic signaling throughout the brain. Brexanolone, the intravenous formulation of allopregnanolone,

was approved by the FDA in 2019 for the treatment of postpartum depression. (59) Furthermore, allopregnanolone analogue, zuranolone, is currently under clinical trials as an oral formulation for postpartum depression and treatment of major depressive disorder in adults, showing promising results. (60)

Also at study, the use of bupropion combined with dextromethorphan is showing promising results in major depressive disorder treatment. Used as a cough suppressant, dextromethorphan is an NMDA receptor antagonist with sedative and dissociative properties that shows rapid-acting antidepressant activity. (57) The rationale for this combination is the fact that bupropion, besides having antidepressant activity, increases the bioavailability of dextromethorphan. A clear advantage of this option is the fact that it didn't show any psychomimetic effects, increased sexual dysfunction, or weight gain in clinical trials. (61)

NV-5138 is another molecule on the horizon. This selective modulator of sestrin leads to the activation of mTORC1 through synaptogenesis in the medial prefrontal cortex. This mechanism of action results in a rapid and targeted antidepressant effect with few adverse effects. (62)

Triple reuptake inhibitors inhibiting the uptake of serotonin, norepinephrine, and dopamine are a novel class of antidepressants that may produce higher efficacy than existing alternatives. Several drugs are under investigation, with some candidates under clinical trials. Recently, the Food and Drug Administration of the United States reviewed and accepted the filing of a new drug application for LY03005, a serotonin-norepinephrine-dopamine triple reuptake inhibitor. (63,64)

Finally, cannabinoid receptors are also being studied as possible targets for new drugs to treat psychological disorders. Cannabidiol's antidepressant anxiolytic, antipsychotic, and antidepressant effects were found in a variety of studies, along with a positive risk-benefit profile. Nonetheless, large-scale studies are still needed to understand the safety and real potential of cannabidiol as a treatment for mood disorders. (65)

As explored above, both recently marketed antidepressants and pipelines in the depression area are promising, but innovative antidepressants will also have adverse

effects that will warrant proper management. It is therefore important that every case is evaluated as one, and treatment is selected and managed according to the patient's characteristics. The next chapter will cover current strategies for treatment optimization, along with future directions of best practices in this area.

3 Benefit-risk ratio optimization

3.1 Basic principles for depression management

It is acknowledged that the benefit-risk ratio of antidepressants falls short of current patients' needs, making it essential to find strategies to harness all of the antidepressants' potential. Effective delivery of antidepressant treatment relies on many factors other than the choice of pharmacologic treatment. The development of a robust strategy takes a combination of a deep assessment of patients' characteristics, choice of non-pharmacological, and, if indicated, pharmacologic options for treatment.

Basic principles for clinical management include a thorough biopsychosocial and psychiatric assessment including differential diagnosis and evaluation for comorbidities such as bipolar disorder, anxiety disorders, and substance use disorders. (14)

An individual and comprehensive management should be built together with the patient. This engagement is crucial for enhancing treatment adherence and reaching optimal results. For this, patient education is essential. He should be aware of all the possible adverse effects, the time needed between starting an antidepressant and having an effect, and the need to continue an antidepressant even with symptom improvement. (36). Self-management, characterized as the individual's ability to manage depression and associated treatments, physical and psychosocial sequelae, and lifestyle modifications, is also a key tool in patient engagement that should be supported by clinicians. (66)

Depression management is often divided into acute and maintenance phases. The acute phase is associated with the main goal of achieving remission and restoration of functioning, whereas maintenance is essentially about preventing recurrence and returning to full functioning and quality of life. Both phases have different main goals and accordingly different pharmacotherapeutic strategies. (66)

Regarding the best approaches for the delivery of care, a stepped care approach is the most commonly used. With stepped care, the least invasive and most effective intervention is provided first, unless the person declines it for any reason. In case the first intervention does not bring benefit, the next appropriate intervention is offered.

The National Institute for Health and Care Excellence (NICE) guidelines for depression management in adults propose four steps of focus of intervention considering pharmacological, psychological, and psychosocial measures, summarized in the table below. (14)

Table 3 The stepped-care model

Focus of the intervention	Nature of the intervention
STEP 4: Severe and complex depression; risk to life; severe self-neglect	Medication, high-intensity psychological interventions, electroconvulsive therapy, crisis service, combined treatments, multiprofessional and inpatient care
STEP 3: Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions; moderate and severe depression	Medication, high-intensity psychological interventions, combined treatments, collaborative care and referral for further assessment and interventions
STEP 2: Persistent subthreshold depressive symptoms; mild to moderate depression	Low-intensity psychosocial interventions, psychological interventions, medication and referral for further assessment and interventions
STEP 1: All known and suspected presentations of depression	Assessment, support, psychoeducation, active monitoring and referral for further assessment and interventions

From: Shepperd and Parker, 2009 (67)

3.2 Therapeutic rationale in antidepressant choice

Many factors should be taken into account when choosing pharmacological options for a mood disorder treatment. While clinicians strive to individualize treatments, clinical guidelines should be used as tools for managing these conditions, always combined with a comprehensive assessment of every patient's situation.

In this chapter, the most current and prestigious guidelines on depression management – such as Canadian Network for Mood and Anxiety Treatment (CANMAT), National Institute for Health and Care Excellence (NICE), and American Psychiatric Association (APA) – as well as other recent relevant publications were reviewed to assess universal best practices to approach depression treatment with antidepressants.

Selecting an antidepressant

Throughout clinical guidelines and publications, it is consensual that before selecting an antidepressant, an analysis of relevant clinical factors should be run. Even though few clinical features show enough evidence to recommend one drug over another, there are a few patient- and medication-related conditions that are important. Patients' preferences, comorbidities, response to previous antidepressant therapy are key factors to take into account. There are also depression specifiers that help selecting treatment and predicting outcomes, such as the presence of sleep disturbances, psychotic or catatonic features, and anxiety.

Regarding antidepressants, their comparative efficacy, tolerability, interactions, cost, and availability must be considered. (34) A combination of clinical and demographic variables has already proven to help to predict treatment outcomes, as seen for example for citalopram in a 2016 study. (68)

First-line treatment recommendations include SSRIs, SNRIs, agomelatine, bupropion, and vortioxetine, followed by second-line TCAs, quetiapine, trazodone, moclobemide, selegiline, levomilnacipran, and vilazodone.

MAOIs are third-line recommendations given their higher side effect burden and potential for food and drug interactions, as well as reboxetine due to its lower efficacy. (34)

Waiting for antidepressant response

It is important to know and inform the patient that antidepressant response is not immediate. Even though some meta-analyses reveal that it can occur in one to two weeks after initiation (36), most studies refer to a 20-30% improvement occurring generally from two to four weeks. (34) When this early improvement happens, response and remission usually occur between six and twelve weeks. The lack of signs of improvement at this stage is a predictor of non-response and non-remission. Both NICE and CANMAT clinical guidelines recommend augmenting the dose if response is not obtained in two to four weeks unless tolerability is a problem. In that case, switching should be the best option. (24, 26)

Managing non-response to antidepressants

Inadequate response to antidepressants is, unfortunately, a common problem that must be addressed. Firstly, measures must be taken in order to understand the cause.

Checking adherence to treatment and side effects is essential. The frequency of appointments with the patient should be increased. Finally, changing the therapeutic strategy ought to be considered. (51)

There are currently two main strategies to manage non-response: switching to a new antidepressant, within or outside the same class, or adding a new one. Both are effective strategies that have advantages, disadvantages, and defined criteria for use, as explored below.

Regarding the switching strategy, switching non-responders to a new antidepressant has been proven to be effective in increasing response and remission rates in several meta-analyses. (69)

To switch between classes or within the same class is still controversial, and evidence shows that switching should be made to a more effective antidepressant. This is the most adequate strategy when it is the first antidepressant trial, when the initial drug has poorly tolerated side effects, shows no response, or if the patient specifically asks to change to another antidepressant. (51)

When selecting a new antidepressant, it is recommended that a different SSRI or a better tolerated newer generation treatment is considered first. Only then switching class for an antidepressant that may be less well tolerated, such as a MAOI or TCA. For drugs with short half-lives, switching is made within one week. Longer half-life drugs such as fluoxetine or non-reversible MAOI require a longer washout period. (51)

In some cases, the best strategy is not to switch antidepressants, but to add a second medication to the initial one. The augmentation strategy is very useful when switching did not improve results, when the antidepressant is well-tolerated, or when there is a partial response. Some specific residual symptoms or side effects can also be targeted with an adjunctive drug. Finally, as the response is usually faster, adjunctive strategy is preferred over switching in severe depression associated with more functional impairment. (34,69)

Selecting an adjunctive drug is linked to an increase in disease burden, so the patient should be well informed and monitored for side effects.

Antipsychotic medications such as aripiprazole and quetiapine have shown the most consistent evidence of efficacy in treatment-resistant depression. (34) There is also evidence for augmentation with lithium as a main strategy for these patients. (70)
Some drugs should not be used to augment an antidepressant with, such as benzodiazepines for more than two weeks due to the risk of dependence, buspirone, carbamazepine, valproate, pindolol, and thyroid hormones, as there is inconsistent evidence of efficacy. (51)

Stopping antidepressant treatment

Achieving symptomatic remission is not a criterion to immediately stopping treatment. Guidelines suggest therapy to be continued for six to nine months, and even up to two years or more if the patient has risk factors for recurrence. (34) The stop must not be abrupt as there is a high risk for discontinuation symptoms. Therefore, the dose should be tapered down over around four weeks. Fluoxetine is an exception to this due to its longer half-life. (51)

3.3 Optimization in special populations

It is well established that antidepressants' effectiveness and safety depend on several different factors. This heterogeneity of response makes customization of therapy to each patient a valuable tool in optimizing antidepressants' benefit-risk ratio.
Special populations, such as the elderly, children, and pregnant women, have specific features that may change response to antidepressants, predisposition for certain adverse effects, and an overall decrease in the benefit-risk ratio. Adverse effects can also become more subjective as undesired effects for one population can be desired for another. To illustrate this, mirtazapine, for example, induces weight gain, but appetite increase can be an advantage in populations with anorexia, and antidepressants that induce somnolence can be useful in some patients with insomnia. This is why an individual clinical assessment and tailoring of pharmacotherapy is key to response and tolerability optimization.
Evidence for efficacy and risk of treatments is often limited in these specific populations, making it important to increase its study and report. Furthermore, existing

evidence should be translated into clinical strategies to manage antidepressant use in special populations.

In the present chapter, special populations' specific features are addressed, and existing evidence and recommendations of treatment are gathered in order to understand the best practices to optimize benefit-risk in these patients.

3.3.1 Childhood and adolescence

Childhood and adolescence are risk periods for the development of mood disorders, and their burden in young people's lives is dangerous. People that develop depression at an early age have an increased probability of developing suicidal ideation, anxiety disorders, substance-related disorders, bipolar disorder, suicidal behavior, and even physical health problems later in their life. (71)

Unfortunately, findings on the efficacy of medicines for depression in children and adolescents differ significantly from adults'. One cause for this is the occurrence of neurodevelopment mechanisms at early ages, that can dysregulate the hypothalamic-pituitary-adrenal axis leading to an exacerbation of negative response to stimuli. Besides this, there is a problem with the statistical power for these ages, since there is a smaller number of trials, and small samples within the trials. Also, psychotherapies used in young patients are mostly adaptations of existing treatments for adults, and may not be suited to the cognitive and emotional characteristics of children and adolescents. (72)

Bearing this in mind, it is of extreme importance to carefully manage treatment in children and adolescents. When it comes to pharmacology interventions, maximizing the benefit-risk ratio through a robust strategy is crucial to achieve beneficial outcomes.

Early recognition of depressive symptoms at young ages is key. Ideally, best practices in depression recognition include various diagnostic tools, symptom severity assessments, and gathering information from different sources like parents and teachers.

Basic principles for depression management must consider the different needs of this specific population. Taking this into account, the NICE guidelines for identification and management of depression in children and young people recommend a stepped care model that provides a framework in which to support both patients and healthcare professionals. (14)

For mild depression, watchful waiting is recommended as an option since a lot of cases recover with no intervention. If no improvement is obtained in the space of two weeks, CBT is recommended. In moderate depression, pharmacological interventions can become an option to add to psychotherapy, or a first-line option if it's severe. (73) The rationale behind this strategy is that there is currently no clear comparative advantage for psychotherapy or pharmacotherapy in the treatment of youth depression. Therefore, the first line in mild to moderate disease is psychotherapy, since the risks are substantially smaller. Within this approach, the most robust efficacy for pediatric and adolescent populations relies on CBT and interpersonal therapy (IPT). (74)

When there is a need to start pharmacological treatment, Canadian, American, and English guidelines agree on identical recommendations for antidepressants' choice. Available evidence points to fluoxetine as the first-choice in a pediatric or adolescent population. Escitalopram, sertraline, and to a lesser extent, citalopram are considered second-line options. TCAs, MAOIs, paroxetine, and venlafaxine are contraindicated in children and young people. (73–75)

During treatment, special attention must be given to the possible increase of suicidality. Clinical trials show a small increase in risk for suicidal ideation and behavior, that tend to occur early in treatment. Nonetheless, the benefit of treatment greatly surpasses risks. Some symptoms associated with treatment initiation or dose change can contribute to this, so every adverse effect should be taken seriously and measures must be taken. (25)

Bearing this in mind, monitoring treatment adherence, effectiveness, and side effects in this specific population is even more important. Patients' progress should be assessed weekly via appointments or telephone contacts during the first month since the beginning of therapy, and then every two weeks. If no progress is achieved within twelve weeks, the next strategy within the stepped care model must be selected. (73)

Maintenance strategies should persist for six to twelve months in patients who do not have any additional risk factors. For patients with a history of more than two depressive episodes or one severe or chronic episode, therapy is recommended to persist for more than this period. (74)

Similarly to antidepressant discontinuation in adults, young populations require a slow taper of dose, considering possible adjustments in case of withdrawal symptoms. Treatment should not be stopped during a stressful time for the patient.

In a scenario where none of the approaches shows efficacy, misdiagnosis or non-adherence to treatment should be considered. Ruling out these hypotheses, non-responders should be switched to a different SSRI, excluding venlafaxine. As for other options available, repetitive transcranial magnetic stimulation may be promising in this population. ECT is not recommended in children and should be performed with extreme caution in young people with severe depression that are resistant to treatment. (74)

3.3.2 Women during pre-natal, post-natal period, and perimenopause

During their life, women are approximately twice as likely to experience depression as men. (76) Depression in women is associated with 50% more burden than men's depression. (75) During and after pregnancy, 12% of women experience depression and 13% anxiety at some point. (77) Additionally, sexual hormone variation in perimenopausal women also increases the risk and burden of mood disorders. (78) Leaving aside what cultural, biological, developmental, and social issues are behind this increased risk, it is of great importance to understand the best ways to manage mental health issues in these subpopulations.

Optimization of the benefit-risk ratio gains a new dimension when talking about depression during pregnancy. The risks of fetal exposure to antidepressants must be balanced with the ones represented by untreated depression. Untreated major depressive episodes have significant risks to offspring's health, leading to an increase in neonatal complications, mild development delays, cognitive, behavioral, and emotional

problems. Furthermore, suffering on women can cause poorer nutrition and medical care, and even dangerous behaviors such as recreational substance misuse. (74)

Even though most antidepressants show no evidence of an increase in major congenital malformations, there are some worries concerning their use during pregnancy. Paroxetine is possibly linked to a small increase in the risk of congenital cardiovascular malformations, even though not causing significant functional impairment in newborns. Poor neonatal adaptation syndrome, characterized by jitteriness, respiratory distress, and excessive crying was observed with an increased frequency in newborns that were exposed to SSRIs during the third trimester, especially with paroxetine, venlafaxine, and fluoxetine. However, this condition is not associated with severe sequelae, is usually time-limited, and resolved with supportive care. Finally, persistent hypertension of the newborn another concern as limited data showed an increased risk when SSRIs are taken late in pregnancy. (79)

In new episodes of mild to moderate depression during pregnancy, guidelines agree that first-line recommendations are non-pharmacological approaches, with higher evidence for CBT and IPT. Pharmacotherapy is established as second-line, except for severe depression where it is a first-choice treatment. These two approaches can be considered together in both cases. (74,79)

Regardless of these recommendations, previous good response or ongoing stability on the medication are also important factors to consider when managing depression during pregnancy, and switching antidepressants for ongoing treatment is usually discouraged. (80)

Regarding antidepressants' choice, key factors to take into account are choosing the lowest risk profile drug, at the lowest effective those, knowing that adjustments may be needed during pregnancy. (77) SSRIs are the recommended class based on efficacy and safety evidenced in major depression disorder outside the perinatal period. Citalopram, escitalopram, and sertraline have shown the most safety and efficacy. Paroxetine is less preferred due to the possible risk increase of cardiovascular malformations. Other SSRIs and first-generation antidepressants lack reproductive studies and are therefore second-line options. (74)

As for the post-natal period, women who were already taking antidepressants are encouraged to maintain treatment while breastfeeding, as infants are five to ten times less exposed to antidepressants than in the uterus. (74,80) Even though there are risks associated with infants' exposure to antidepressants, the nutritional and immunologic advantages of breastfeeding outweigh these concerns. (79)

Women should be properly supported and monitored for any symptoms throughout pregnancy and the post-natal period, as well as the neonate. Adherence ought to be assessed and if a woman decides to stop medication, healthcare professionals should ensure she is aware of risks associated for her, the fetus, and the baby. It is also important to discuss the possibility of starting a psychological intervention or restarting the medication. (77)

In summary, the benefits of antidepressants outweigh all of the above-stated risks if a pregnant woman has a psychiatric condition that requires pharmacological therapy. (79)

Another period of increased risk of depression during a woman's lifetime is the transition to menopause, as well as the post-menopause period. Associated with disturbing symptoms such as decreased libido, hot flashes, sleep disturbances, and vaginal dryness, women also have higher risk of developing anxiety and depression, either in recurrence or in first-time episodes. (74)

Having had previous depressive episodes, premenstrual syndrome, postpartum depression, hot flashes, nocturnal sweating, insomnia, or an elevated body mass index, represent risk factors for developing perimenopause depression.

As for the management of this condition, antidepressants are also first-line recommendations. However, post-menopausal depression is usually more severe and more resistant to treatment with antidepressants when compared to women before menopause. Combination with hormone therapy, specifically transdermal estradiol, improves outcomes, being also a first-line recommendation. (81)

Regarding the choice of antidepressants, there is no evidence of superiority of specific drugs for women in perimenopause. Previous response to an antidepressant should be assessed if it is the case of recurrent episodes, and it should guide the decision of first-line treatment. If there is no information of previous depressive episodes or use of

antidepressants, evidence supports the use of newer-generation antidepressants. Randomized trials specifically tested desvenlafaxine's efficacy in peri- and post-menopausal women with depression, showing for both groups a higher efficacy than placebo. Smaller studies have shown efficacy for citalopram, duloxetine, escitalopram, mirtazapine, quetiapine, and venlafaxine. (74,78)

When selecting an antidepressant for this specific population, it is also important to examine data on adverse effects, since many women are already experiencing sexual dysfunction and changes in metabolism. When this is the case, clinicians should opt for drugs that have fewer interferences with weight and sexual function. (78)

3.3.3 The elderly

The term late-life depression designates depression within the population of sixty years and older. It includes patients whose depressive disorder presented earlier in life and is recurring in late life, and patients who are having depression for the first time in late life. Late-onset depression is associated with a worse prognosis, higher medical comorbidity, cognitive impairment, and mortality when compared to mid-life set depression. (74) As it often accompanies serious medical issues, depression in the elderly is under-recognized and under-treated.

Depression is not a natural result of aging. Nonetheless, there is an increase of risk factors for mental illness that come with age. Cognitive impairment, social isolation, uncontrolled pain, and psychosocial adversity are the main characteristics of this population that lead to the onset of late-life depression. But beyond these adversities, there are natural and pathological changes such as arteriosclerosis, inflammatory, endocrine, and immune processes that increase vulnerability to depression. (82)

Pharmacokinetic changes with aging may change the rate of absorption, bioavailability, and half-life of most antidepressants, which presents another challenge for this specific population. As the older population is often polymedicated, drug-drug interactions are an issue. Side effects are also increased when compared to younger patients, and otherwise rare adverse effects are more common in the elderly. (74)

All of the above-referred factors worsen the prognosis of depression in the elderly and make it difficult to manage. Response to antidepressants is lower when compared to younger patients, and effective psychosocial approaches are complex and of difficult access to older people. (83) That being so, specialized and effective strategies must be used in order to increase adherence and effectiveness of treatment.

An initial assessment must focus on the identification of medication intake or presence of illnesses that might predispose to depression. Then, addressing comorbidities, individualizing pharmacologic and non-pharmacologic treatment, and closely monitor tolerance and effectiveness are crucial to successful management of depression. (82)

The relatively small number of clinical trials including people aged over sixty years leads to a dearth of evidence, and some divergences of conclusions between randomized clinical trials and current clinical practice make it difficult to do specific recommendations. Clinical guidelines recommend an evidence-informed rather than evidence-based treatment approach. (74)

The choice of treatment holds many factors, namely the type and duration profile of the depression, patients preference, level of access, and specific contraindications to medication.

For subthreshold or mild depression, psychotherapy may be used singly. For moderate to severe cases, pharmacotherapy is consensually the first-line recommendation. A combination of both showed efficacy in chronic cases. (51,74,82)

When a pharmacologic approach is indicated, it must be selected bearing in mind all the particular features of each case. In adverse effects monitoring, particular attention must be paid to falls, hyponatremia, and gastrointestinal bleeding. Prescribing a gastroprotective should be considered if the patient is taking non-steroidal anti-inflammatory drugs or aspirin. (51) Additionally, side effects as bone loss, neuroleptic malignant syndrome, serotonin syndrome, and extrapyramidal effects, which are rare in adults, can become more common in late-life depression. (74)

SSRIs and SNRIs are the antidepressants of choice for late-life depression. Sertraline, paroxetine, and duloxetine showed the most efficacy. Aripiprazole augmentation is recommended as a safe and effective option for treatment-resistant depression. (82)

As for posology, the initial dose given to the elderly should be low and titrated to similar to those used in younger adults. Antidepressants response might take longer in the elderly, occurring between eight to twelve or even sixteen weeks of therapy. (82)

There is evidence that supports the efficacy of continuation and maintenance treatment in late-life depression. When determining the duration of maintenance treatment, the number of previous episodes, residual symptoms, previous tolerability to antidepressants, medical burden, and patient preferences must be taken into account. (83)

In this population, a non-pharmacological approach is highly recommended either singly in mild depression or in combination with antidepressants in more severe and chronic cases. Problem-solving therapy has strong evidence in reducing depression rating score rates and disability. (74) CBT and IPT are also recommended in guidelines, either individually or in group sessions. (75)

3.4 Pharmacogenetics in therapy optimization

The previous chapter explored how the benefit-risk ratio of antidepressants could be optimized by tailoring pharmacological interventions to each patient. In this chapter, the individuality of every patient is even more in focus.

It is known that genetic variation affects the efficacy and safety of a medicine, influencing both its pharmacokinetics and pharmacodynamics. To address this challenge, pharmacogenomic assessments are emerging in different therapeutic areas to develop a personalized approach to drug selection. (84) Guiding antidepressant therapy through CYP enzymes pharmacogenomic testing is showing promising results. (34)

In psychiatry, interindividual differences in treatment outcomes are associated with CYP2D6 or CYP2C19 polymorphisms. (85) Most antidepressants are metabolized in

the liver by these enzymes. Paroxetine and fluvoxamine are metabolized by CYP2D6, and variations in its activity may lead to higher or lower levels of these drugs. Fluoxetine is metabolized both by CYP2D6 and CYP2C19 to active enantiomers. In citalopram and escitalopram metabolism, CYP2C19 converts them to compounds with less activity. Sertraline is metabolized mainly by CYP2C19, but also by CYP2D6 and other cytochrome P450 enzymes.

In summary, variations in CYP2C19 may result in altered drug exposure for citalopram, escitalopram, and sertraline, while CYP2D6 polymorphisms have a higher impact on paroxetine, fluvoxamine, fluoxetine, and sertraline. (85)

In such cases, biotransformation is altered, and these patients may be predisposed to a lack of antidepressant efficacy or more severe adverse effects. Pharmacogenetic testing could guide SSRI therapy and potentially improve treatment response, as well as decrease adverse effects occurrence.

Overall, available evidence points to the efficacy of pharmacogenetic testing to detect fast and slow metabolizers that can have resistance to treatment or more predisposition to adverse effects. CANMAT guidelines recognize its utility in individuals who cannot tolerate minimum antidepressant doses, are high doses treatment-resistant, or nonadherent to therapy. They do not recommend its routine use because even though there is evidence of improvement in outcomes in depression patients, large-scale random clinical trials were lacking. (34)

In 2019, a recent large-scale randomized control trial concluded that pharmacogenetic testing significantly improves response and remission rates for difficult-to-treat depression patients. The data also suggested that there was achievement of sustained remission, which is the ideal goal of major depressive disorder treatment. (84)

A recent study also showed potential in the use of pharmacogenetics assessment to guide the prescription of pharmacotherapy alone versus pharmacotherapy with psychotherapy in potential non-responders for treatment with antidepressants. (86)

As for the pediatric population, a review showed that there is only modest evidence for many of the gene-antidepressant associations with moderate to strong evidence in

adults. Further research is needed to confirm gene-antidepressant associations in children and adolescents since antidepressant prescription is rather common in these populations. (87)

When the problem of dearth of evidence is tackled, there will still be some challenges to face before implementing routine pharmacogenetic testing for use of antidepressants. Firstly, there is not a standardized method for genotyping across laboratories, as different platforms are in use. This makes it difficult to compare results and get clear indications from guidelines.

Translating existent evidence into clinical measures represents another pressing need. There are currently guidelines with recommendations of posology adjustments in patients with polymorphisms, such as FDA, Clinical Pharmacogenetics Implementation Consortium (CPIC), and Pharmacogenomics Knowledge Base (PharmGKB) lists. Nevertheless, better harmonization is still called for. (88)

Finally, cost-effectiveness is of major importance. Affordability and access to combinatorial testing for patients is naturally a limitation to its routine implementation. However, with different factors weighted, pharmacogenetic testing implementation could actually reduce health-care related costs by preventing adverse reactions, regular drug level monitoring, and their associated cost.

A recent study conducted in the United States of America predicted a savings of $3,962 annually per patient with pharmacogenetic-guided medication management. (89) In Europe, pharmacogenetic testing is way less expensive, making it even more accessible and helping to reduce health-related expenses. Besides, the test is taken once in a lifetime which is an advantage when compared to continuously measuring drug concentrations. (88)

The large European trial Ubiquitous PGx is investigating a more cost-effective approach, where each patient would have a DNA passport for medication with polymorphic gene information and specific recommendations of action. This would avoid that every clinical field would have to concern about cost-effectiveness, increasing the benefit of pharmacogenetic tests. (90)

As the era of precision medicine is evolving, a future drop in genotyping costs and availability of genetic data in large databases could lead to the future development of cost-effective genetic predictors. With pharmacogenetic testing being a relatively new idea, more real-world studies are necessary to assess cost-effectiveness, benefit, and what other enzymes receptors or drug transporters could support clinicians targeting therapies and integrating pharmacogenetic information mental illness management. (88)

3.5 The pharmacist's role in treatment optimization

As addressed in this monography, when it comes to antidepressants' benefit-risk ratio, there is still room for improvement. The rate of non-adherence to antidepressant therapy is higher than other types of medication, with numbers as high as 56%. (18) Depression remission rates with SSRIs are below 40%. (91) Therapy-related issues include delay onset of clinical results, risks in case of sudden pharmacotherapy abruption, several adverse drug reactions, and interactions.

The solution for reaching better results lies not only in the individualization of therapy but also in close accompaniment by multidisciplinary teams. It is therefore important to recognize the key role of healthcare professionals in assisting and educating patients around mental illness, and the value that pharmacists in particular have in the management of treatment and its optimization.

With the valuable tool that is the large network of community pharmacies, pharmacists are in a prime position to directly impact mental health care. Screening, educating, providing valuable resources, and evaluating drug-related problems, are part of a pharmacist's responsibilities. (92) Providing pharmaceutical care includes collecting patients' specific information, analyzing it to detect drug-related problems, assess effectiveness and safety of therapy, patient's adherence, and compliance. These services must be provided from the start of therapy until stopping it is indicated. (10)

Providing pharmaceutical care services can considerably improve patient outcomes. Increase in adherence, quality-of-life, and therapy effectiveness were reported in several recent studies. (93–96) Besides, another study associated collaboration between

clinical pharmacists and physicians with improvement of clinical outcomes and a decrease in hospitalizations. (97) Given the proximity of pharmacists to the patients, they play a major role in mental health issues symptom detection, either by direct observation or with screening tools such as the Patient Health Questionnaire, Well-Being Index, or the Hamilton Depression Rating Scale. (92) Screening for depression in community pharmacies was proven to be useful in the early detection of depressive symptoms and is feasible with minimal material and personnel. However, low response rates of prescribers is still an issue that needs to be tackled. (98)

Given all of this evidence, the question remains as to how adequately deliver pharmaceutical care to patients with mental issues. Even though there is not a universal detailed guideline providing algorithms and instructions on pharmaceutical care delivery, there are already some documents giving recommendations on how pharmacists can properly detect, educate and monitor patients' pharmacotherapy. According to these existing documents, the most important aspects of how to manage a patient with depression in a community pharmacy setting are explored below.

3.5.1 Initial visit

The first step towards assisting a patient with depression in their treatment is to be aware of all their specific information. This data must be collected and then analyzed in order to detect the actual and potential drug-related problems.

Communication is key both to obtain accurate information and advise the patient in a way that is useful to him. A recent guideline gives recommendations on how to communicate with these patients, suggesting asking open and closed questions, avoiding asking confusing questions and interrupting the patient, showing empathy and sympathy for the person. (99)

Educating patients and advising them about the prescribed medicines are also crucial in the management of depression treatment. The patient should be fully aware of the main symptoms of the disease and details regarding the prescribed treatment. Using clear and easily understandable language, the pharmacist ought to explain the therapeutic scheme and the mechanism of action of the antidepressant. The patient must also be warned

about the possible adverse effects, the onset of action of the prescribed drug, and informed that the therapy is continuous, having the risk of severe adverse effects if stopped abruptly without a specific recommendation from the physician. (10)

Materials such as informative leaflets are a valuable and relatively easy way of providing this type of information. Nevertheless, suitability varies according to patients' characteristics. The range of questions covered, depth of detail in answering a particular question and the language used are key factors to adapt considering the target of the information. (100)

Another useful way to educate the patients is to provide a list of local support groups and mental-health providers, such as psychiatrists, psychotherapists, or local health departments. Providing hotline numbers can also be helpful in emergencies (92)

Recommending additional non-pharmacological measures can also induce outcomes improvement. Cognitive-behavioral therapy, regular physical activity, sleep hygiene, healthy eating, and cognitive bibliotherapy have proven benefits in patients with depression. (10)

Combined, all of this sharing of information strategies by pharmacists have great potential to improve community health and even decrease stigma around mental health problems.

Besides informing and educating patients on rational use of antidepressants, pharmacists have the pharmacotherapeutic knowledge to, together with physicians, caregivers, and patients, develop an individualized therapeutic plan. This is of major importance as it improves efficacy outcomes and increases the level of adherence.

For the development of this individualized plan, the pharmacist should firstly assess patients' needs. The prescribed drug, dose, and duration of treatment must be checked for adjustment to patients' characteristics, and possible contraindications or interactions must be ruled out. If there is any drug-related problem, contact must be established with the prescriber. (100)

After this assessment, realistic and consistent pharmacotherapeutic goals must be defined for the patient. These goals are ideally measurable and will then be monitored

in follow-up visits to the pharmacy. With all of this in mind, a pharmacotherapeutic regimen is set, in compliance with medication use policies and patient's capabilities and financial resources. Follow-up visits must be scheduled to help monitor adherence, drug-related problems, and efficacy outcomes. (101)

3.5.2 Follow-up visits

Engaging patients in follow-up is crucial to allow therapeutic monitoring and optimize patients' treatment. In a follow-up visit to the pharmacy, pharmacists have the opportunity to identify, prevent and even solve drug-related problems.

Medication review is an essential pharmaceutical care service. In a community pharmacy setting, pharmacists should search for potential interactions, inappropriate prescription, therapeutic duplication, allergies, adverse drug events, inadequate use of medicines, or lack of education around the disease and medication. (101)

All of the above-referred drug-related problems can be recognized by the pharmacist in a dialogue with the patient. Some of these issues, such as severe adverse effects or interactions, are serious and patients should be directed to talk to their psychiatrist. Weight gain, sexual dysfunction, tachycardia, migraines, or suicidal ideation are examples of symptoms that should be reported to a physician and may need dose adjustment or therapy switching.

Nonetheless, in several cases, pharmacists can be helpful by giving direct solutions. For antidepressants with sedating effects, patients can be advised to take them at bedtime. For orthostatic hypotension, reducing caffeine, avoiding standing up abruptly and drinking water are simple actions that can increase tolerability. Nausea can be reduced by taking small portions of food throughout the day or taking the medicines after a meal. All of these recommendations may seem simple but are of extreme importance to increase the benefit-risk ratio of antidepressants and increase adherence to therapy. (10)

Finally, another important aspect is when and how to stop the medication. It is part of a pharmacist's role to ensure that patients don't take medication for longer than necessary, and on the other hand that they don't stop the treatment without indication.

4 Conclusions

With mental health conditions getting worse worldwide, the need for new approaches to mental health issues is undeniable. Discovering new mechanisms of action and new molecules is urgent to effectively fight the pandemic represented by mental health disorders.

Antidepressants' benefit-risk ratio is still far from optimal given the present needs of the population. In the present dissertation, a literature review of currently used antidepressants showed superiority of the safety profile of newer generation SSRIs, NSNRIs, and atypical antidepressants when compared to first-generation antidepressants MAOIs and TCAs. Nonetheless, a great number of patients still struggle with adverse effects that limit their quality of life. From gastrointestinal effects, sexual dysfunction, sleep, metabolic and affective disturbances, up to arrhythmia and increase of suicidality, antidepressants have a relatively unsatisfactory safety profile. Efficacy assessment showed that even though antidepressants are the most effective approach to treat mood disorders such as depression, a great percentage of patients show little to no response to initial treatment. There are conclusions regarding the comparative efficacy of antidepressants, showing superiority for newer generation drugs escitalopram, mirtazapine, sertraline, venlafaxine, agomelatine, and citalopram.

As for new therapeutic options, the glutamatergic pathway is showing potential with alternative targets for the traditional monoamine receptors. Fast-acting antidepressants such as esketamine recently entered the market, and other drugs acting on NMDA receptors are at study and may be commercialized in the short term. Additionally, GABA receptors are promising targets for antidepressants development. Allopregnanolone is already approved and similar drugs are in clinical trial phases.

But even though new antidepressants are on the horizon, it is essential to take the best benefit of available therapeutic options. It is possible to improve the benefit-risk ratio by managing treatment in an individualized way and with a close monitoring approach. The present dissertation explored the different strategies that are adopted in different countries and contexts to reduce the risk of adverse effects, improve adherence and efficacy of antidepressants, with a focus on treatment of depressive disorders.

To select an antidepressant for a patient, available data corroborates the great significance of running an individualized analysis of relevant clinical factors. Overall, first-line recommendations include SSRIs, SNRIs, agomelatine, bupropion, and vortioxetine. However, patients' preferences, comorbidities, and response to previous antidepressant therapy are key factors to take into account. It is also important to bear in mind, as well as inform the patient, that antidepressants results are not immediate, taking usually from two to four weeks. Recognizing resistance to treatment and adjusting therapy may improve adherence, efficacy, and safety of antidepressants. Augmentation and switching are two effective strategies to manage the lack of response to pharmacotherapy. There is currently no superiority of one over another approach evidenced. Advantages, disadvantages, and clinical context must be evaluated to select switching or augmentation therapy.

Furthermore, there are special populations, such as the elderly, children, and pregnant women that have important clinical specifiers. These specific characteristics may change response to antidepressants, predisposition for certain adverse effects, and an overall decrease in the benefit-risk ratio if the therapy is not tailored to the patient. Available evidence and recommendations of treatment were gathered to determine the best practices to optimize benefit-risk in these patients.

In young patients, evidence on antidepressants effects is limited when compared to adults. Careful management is necessary, and antidepressants are only recommended in more severe cases as there is no clear comparative advantage for psychotherapy or pharmacotherapy in this population. Fluoxetine is the first-line pharmacological option for children and adolescents.

Women have different periods of their lives where there is an increased risk for depressive disorders. During pregnancy, the risks of untreated depression must be balanced with those associated with fetal exposure to antidepressants. There is evidence of risk of poor neonatal adaptation syndrome, congenital cardiovascular malformations, and persistent hypertension of the newborn. However, if a pregnant woman has a psychiatric condition that requires pharmacological therapy, the benefits of treatment clearly outweigh all of the stated risks. As for the post-natal period, women who were

already taking antidepressants are encouraged to maintain treatment while breastfeeding.

During perimenopause, the use of antidepressants is recommended in association with hormonal therapy, in women who have no contraindications for these approaches. As many women experience menopausal symptoms, it may be important to select an antidepressant that has few interferences with sexual function or weight.

The elderly represent a population with many specificities. People over sixty years old are in many cases polymedicated, have comorbidities, and special vulnerability to some adverse effects. Recommendations for late-life depression include pharmacotherapy in moderate to severe cases, and psychotherapy for mild depression. Sertraline, paroxetine, and duloxetine showed the most efficacy, but it is key to look for possible drug-drug interactions and vulnerability to certain adverse effects. Particular attention must be paid to falls, hyponatremia, and gastrointestinal bleeding.

When it comes to treatment customization, pharmacogenetics is a field of extreme importance. Guiding antidepressant therapy through cytochromes P450 enzymes pharmacogenomic testing is showing promising results. Interindividual variation to antidepressants response was found mostly associated with CYP2D6 and CYP2C19 polymorphisms. Available evidence points to the improvement of efficacy when pharmacogenetic testing is used to detect fast and slow metabolizers that can have resistance to treatment or more predisposition to adverse effects. To incorporate this type of testing in clinical recommendations, more large-scale studies are needed, as well as a clear understanding of the cost-effectiveness of this approach.

Finally, the solution for reaching better results lies not only in the individualization of therapy but also in close accompaniment by multidisciplinary teams. Pharmacists have a major role in reducing drug-related problems, and providing pharmaceutical care services considerably improves patient outcomes.

Pharmacists have the full capacity to detect, educate and monitor patients' pharmacotherapy through clear communication, educational material providing, and advising on pharmacologic and non-pharmacological approaches. Developing an

individualized therapeutic plan together with physicians, caregivers and patients also showed to improve efficacy outcomes and increase levels of adherence. After this initial approach, engaging patients in follow-up helps to monitor for adverse effects and maintain treatment adherence.

In conclusion, all of the referred strategies are of utmost importance to maximize the benefit-risk ratio of antidepressants, and must not be overlooked when managing patients with mental disorders. Individualization of therapy is key to improve outcomes and should be incorporated in the management of these disturbances. Future directions include standardization of methods to select and monitor pharmacotherapy, the association of non-pharmacological measures, and multidisciplinary work between physicians, pharmacists, patients, and caregivers.

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